GeneMAP

Genetic Medicine of African Populations

Why we should invest in 3MAG: sequencing 3 million African Genomes

Ambroise Wonkam, MD, PhD

Professor and Deputy Dean Research
GeneMAP Director

Three reasons to invest in African Genomic Variations:

1- Ancestry

2- Ecology

3- Equity

-1.1-

African Ancestry: missing variants

Missing African Variants in the Human Reference Genome

Assembly of a pan-genome from deep sequencing of 910 humans of African descent

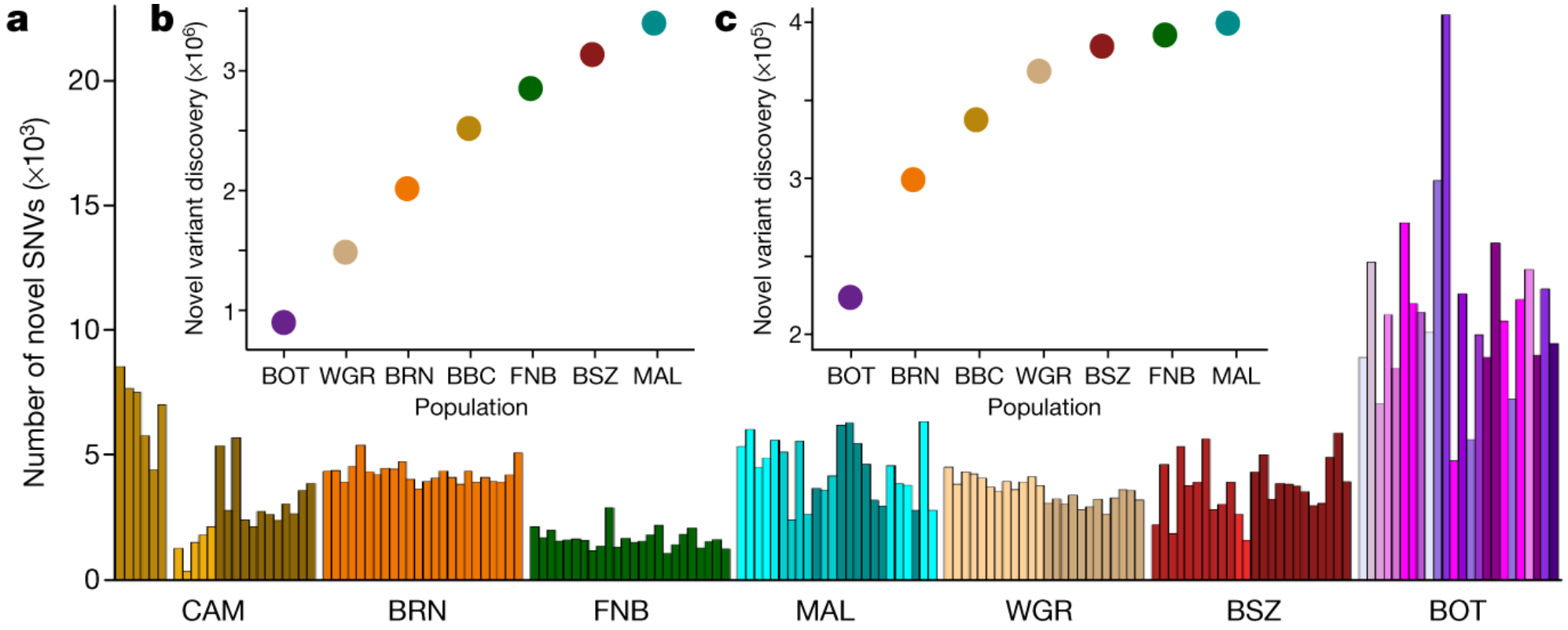
Rachel M. Sherman[1,2,*], Juliet Forman[1,3], Valentin Antonescu[1], Daniela Puiu[1], Michelle

African pan-genome contains ~10% more DNA than the current human reference genome.

Nat Genet. 2019 January ; 51(1): 30–35. doi:10.1038/s41588-018-0273-y.

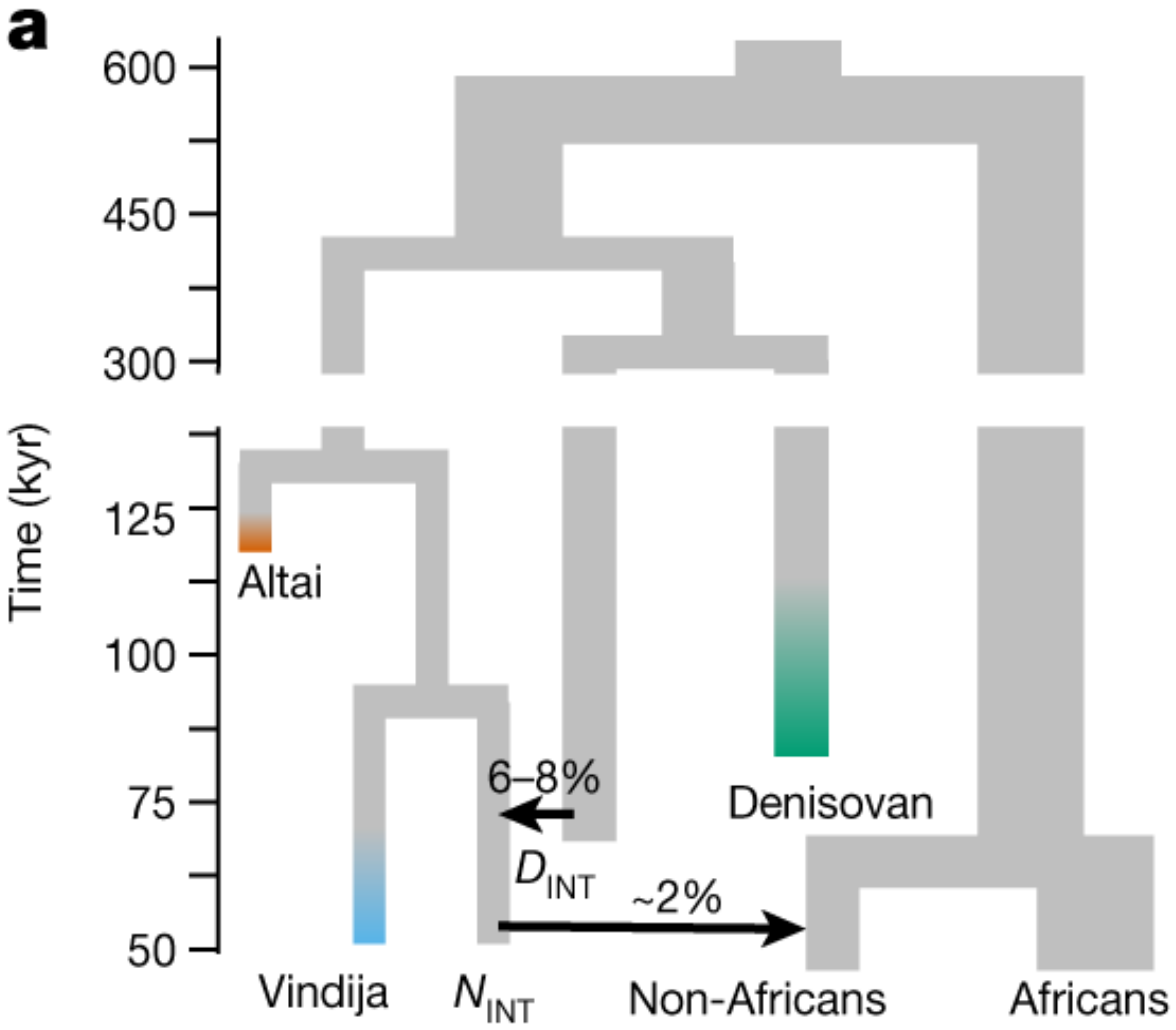
Missing African Variants in the Human Reference Genome

H3Africa dataset: 3.4 million SNVs Novel variation



Nature volume 586, pages741–748(2020)

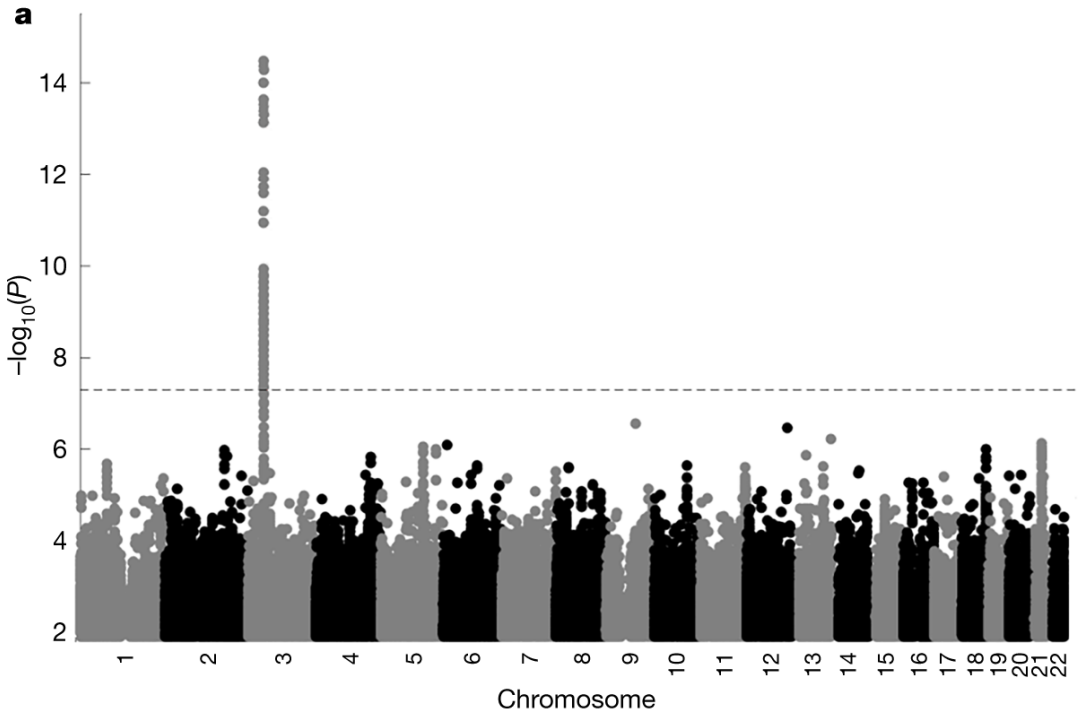
Unknown Archaic Human DNA in Africans Genomes



Durvasula & Sankararaman, Sci Adv. 2020 Feb; 6(7): eaax5097.

Archaic Human DNA, Health and Diseases

Neanderthal DNA and Covid -19



- **Major genetic risk factor for severe COVID-19**

Zeberg & Pääbo , Nature, 2020 Nov;587(7835):610-612

Others associated traits and diseases

- Dermatological phenotypes
- Neuro-psychiatric disorders
- Immunological functions

Skov, L. et al. *Nature.* **582,** 78-83, (2020)
Almarri et al. *Cell* 2020, 182, 1–11
Dannemann & Kelso. *Am J Hum Genet*. 2017; 101: 578–5
Simonti et al., *Science* 2016 351, 6274: 737-741

Some Variants are more frequents in Africans

PCSK9: Frequent nonsense mutations *and* Low LDL cholesterol in Africans

- Mutations were common in African Americans (average 2%)

  but rare in European Americans (<0.1%)

- Associated with a 40% reduction in plasma levels of LDL cholesterol

- ***PCSK9:*** privileged target for dyslipidaemias therapeutics

Cohen et al. *Nature Genetics* 2005, **37:** 161–165

Some Variants are Specific to Africans

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-10967-7 OPEN

ZRANB3 is an African-specific type 2 diabetes locus associated with beta-cell mass and insulin response

Adebowale A. Adeyemo[1,22], Norann A. Zaghloul[2,3,22], Guanjie Chen[1], Ayo P. Doumatey[1], Carmen C. Leitch[2], Timothy L. Hostelley[2], Jessica E. Nesmith[2], Jie Zhou[1], Amy R. Bentley[1], Daniel Shriner[1], Olufemi Fasanmade[4], Godfrey Okafor[5], Benjamin Eghan Jr[6], Kofi Agyenim-Boateng[6], Settara Chandrasekharappa[7], Jokotade Adeleye[8], William Balogun[8], Samuel Owusu[9], Albert Amoah[9], Joseph Acheampong[6], Thomas Johnson[4], Johnnie Oli[5], Clement Adebamowo[10], South Africa Zulu Type 2 Diabetes Case-Control Study, Francis Collins[12], Georgia Dunston[13] & Charles N. Rotimi[1]

-1.2-

African Ancestry and Monogenic diseases: Allelic and locus heterogeneity

Genes and Variants for monogenic conditions varies in Africans

- **Huntington disease**

Europeans: 99% triplet expansion in *HTT*
Africans : 67% in *HTT, and* 33% *JPH3*

- **Cystic fribrosis**

CFTR 3120+1G>A variant that is the most common causal t in African CF patients

Krause, A., et al *Annu Rev Genomics Hum Genet* **19**, 149-175 (2018)

- **Congenital Hearing Impairment**

Europeans: 50 % variants in *GJB2*
Most Africans: 0%

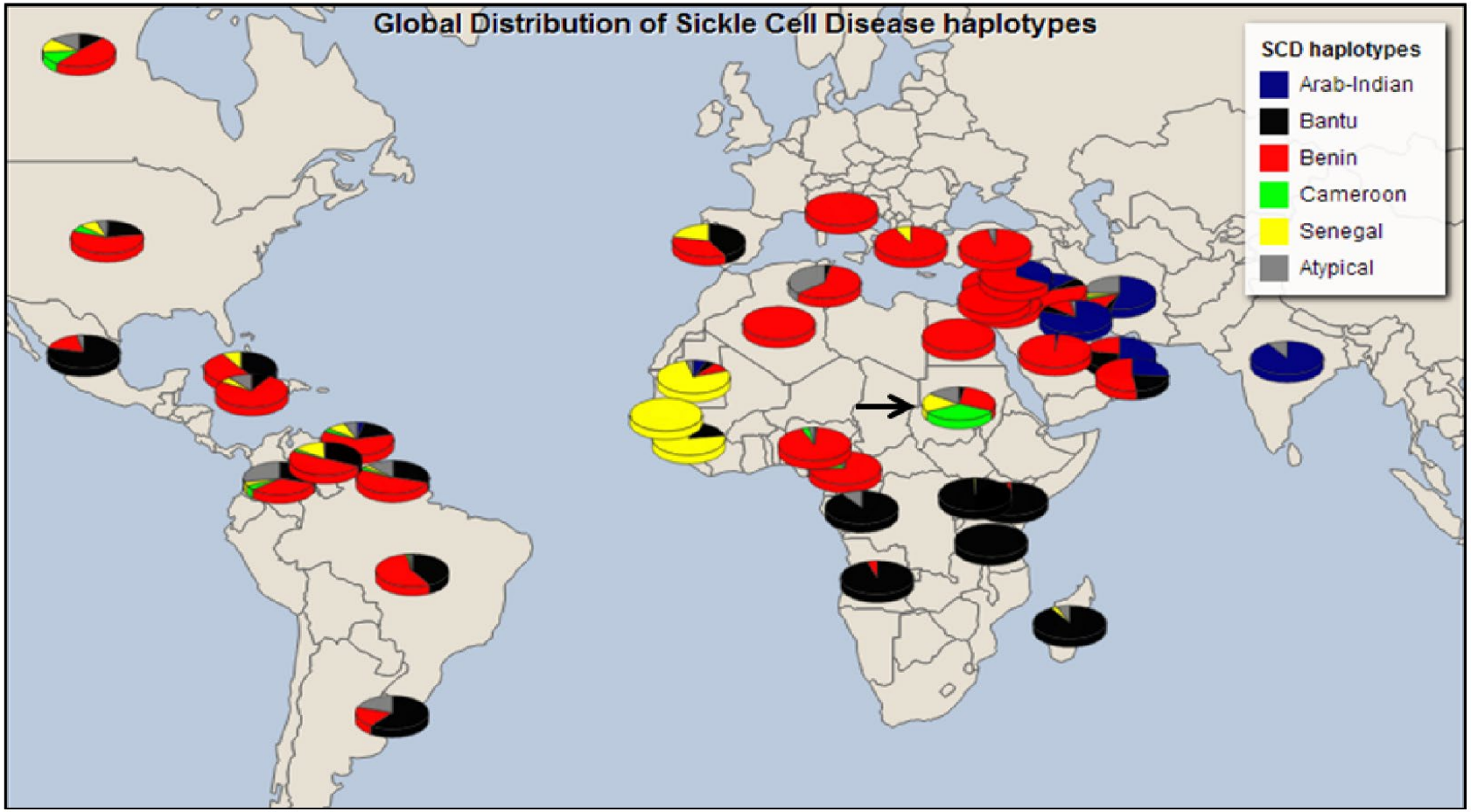
Genes **2019**, *10*, 844; doi:10.3390/genes10110844

-2-

Africa's Ecology:

Adaptation signals and natural selections in African genomes

Malaria and Single Origin of Sickle Cell Mutations



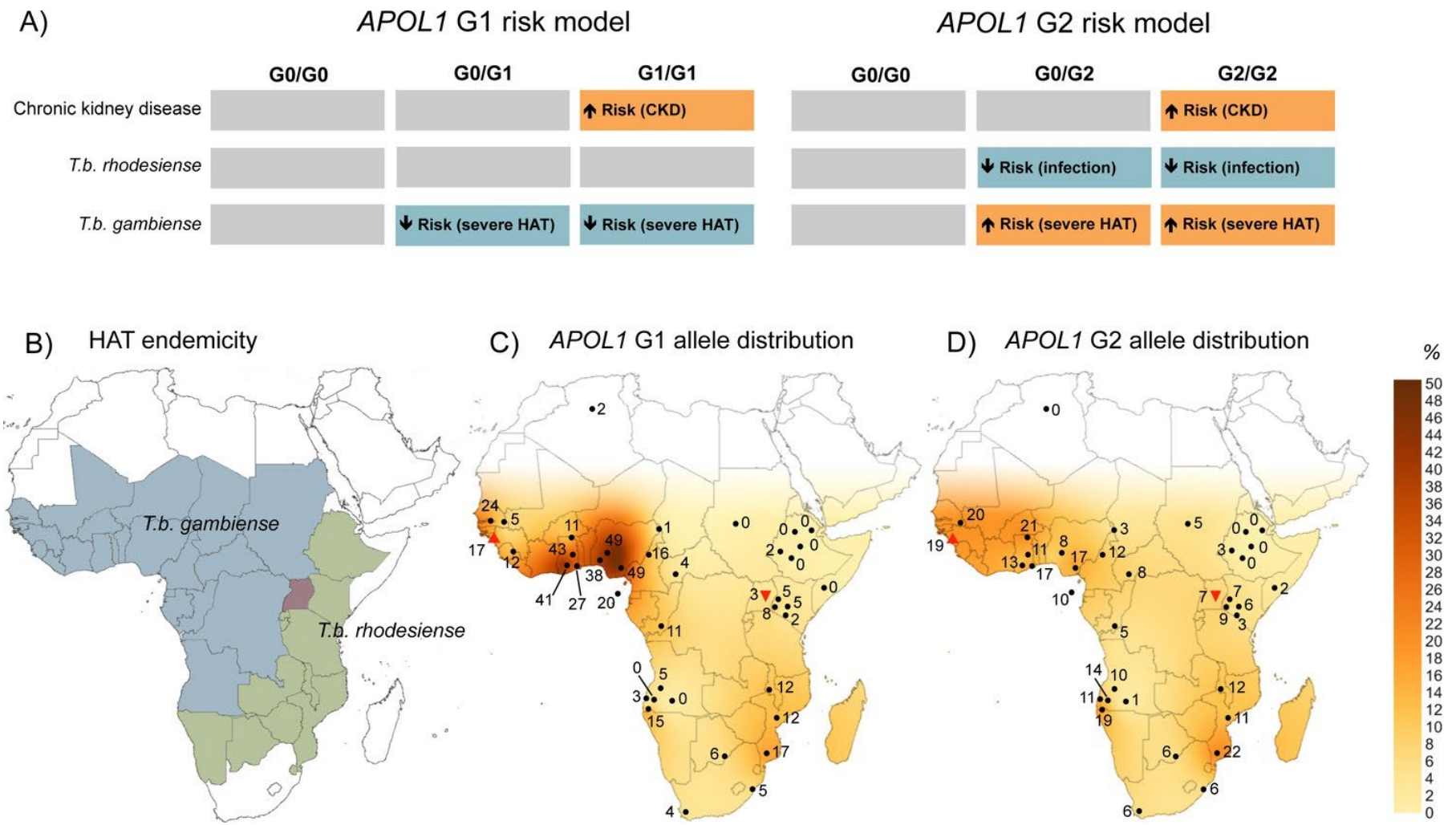
Bitoungui …. et Wonkam,
OMICS. 2015 Mar;19(3):171-9.

ARTICLE

Whole-Genome-Sequence-Based Haplotypes Reveal Single Origin of the Sickle Allele during the Holocene Wet Phase

Daniel Shriner[1] and Charles N. Rotimi[1,*]

Trypanosomes and *APOL1*



Cooper et al. eLife 2017;6:e25461

Association of Trypanolytic ApoL1 Variants with Kidney Disease in African Americans

Giulio Genovese,[1,2]* David J. Friedman,[1,3]* Michael D. Ross,[4] Laurence Lecordier,[5]

SCIENCE VOL 329 13 AUGUST 2010

bjh research paper

Clinical and genetic predictors of renal dysfunctions in sickle cell anaemia in Cameroon

Amy Geard,[1] Gift D. Pule,[1] Bernard Chetcha Chemegni,[2] Valentina J. Ngo Bitoungui,[2] Andre P. Kengne,[3] Emile R. Chimusa[1] and Ambroise Wonkam[1]

Summary

Micro-albuminuria and glomerular hyperfiltration are primary indicators of renal dysfunctions in Sickle Cell Disease (SCD), with more severe manifestations previously associated with variants in *APOL1* and *HMOX1* among

Association of Genetic Polymorphisms of *TGF-β1*, *HMOX1*, and *APOL1* With CKD in Nigerian Patients With and Without HIV

Udeme E. Ekrikpo, Khuthala Mnika, Emmanuel E. Effa, Samuel O. Ajayi, Chimezie Okwuonu, Bala Waziri, Aminu Bello, Collet Dandara, Andre P. Kengne, Ambroise Wonkam, and Ikechi Okpechi

Dengue Fever and Natural Selection

OSBPL10, *RXRA* and lipid metabolism confer African-ancestry protection against dengue haemorrhagic fever in admixed Cubans

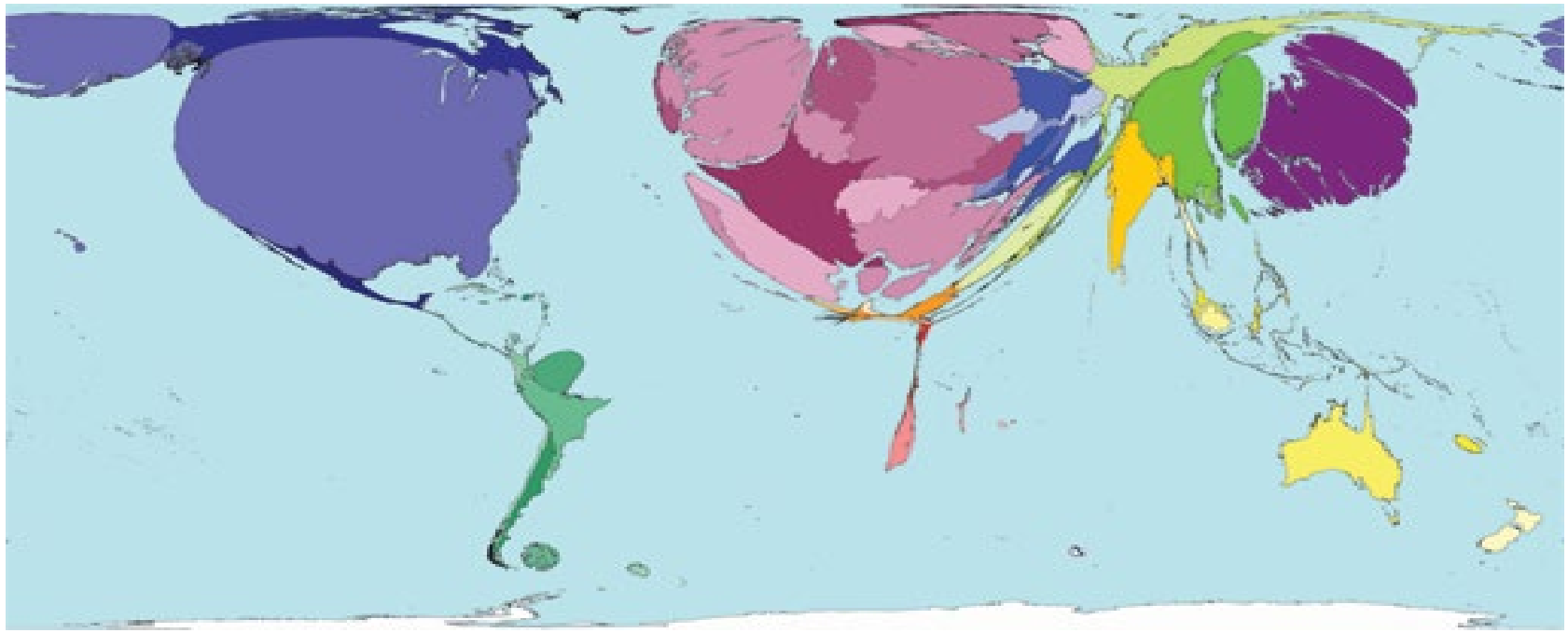
Beatriz Sierra[1☯*], Petr Triska[2,3,4☯], Pedro Soares[3], Gissel Garcia[1], Ana B. Perez[1],

PLOS Pathogens | DOI:10.1371/journal.ppat.1006220 February 27, 2017

Africans Genomics Study is a Scientific Imperative

-3-
Africans Genomics Study: How to Address the Equity Imperative?

Africa: Innovation & Wealth creation

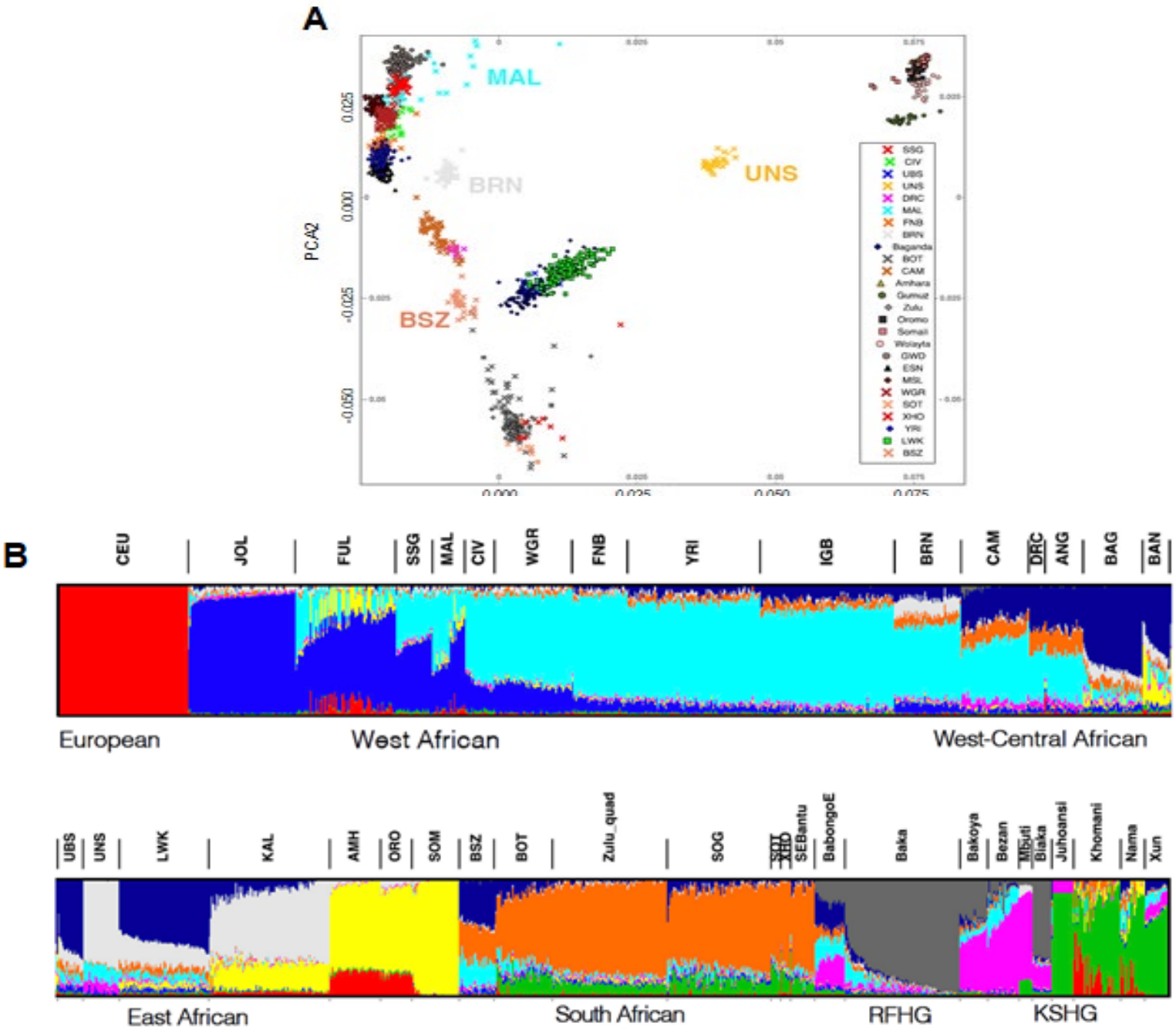


- Africa is home to 15% of the world's population
- 5% of the world's gross domestic product (GDP)
- 1.3% of global investment in research and development

- 300000 of Human Genomic History


H3
H3Africa
Human Heredity and Health in Africa

H3Africa: African Populations Structures

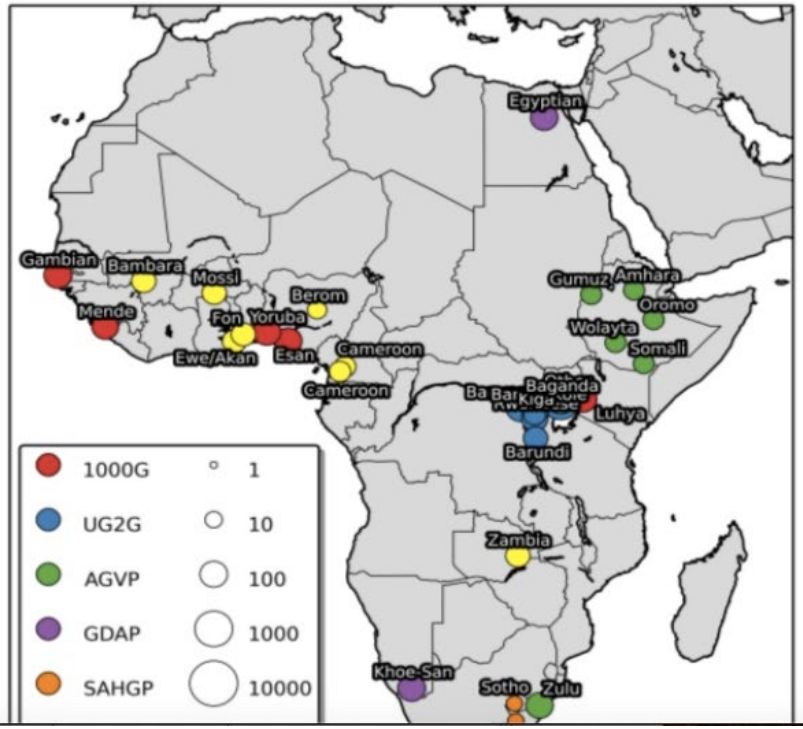


H3Africa Consortium , Nature 2020

H3Africa CHIP Design

Sample size and distribution

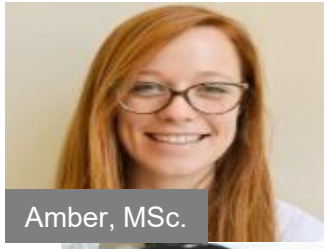
Source	Number of samples
GDAP	204
UG2G	2000
AGVP	320
1000G	507
TrypanoGEN	212
Baylor	348
SAHGP	16
Total	3607

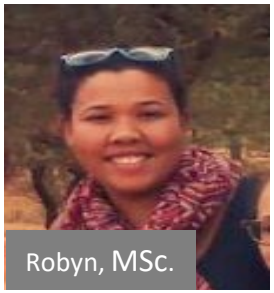


2.5M SNPs, 700’000 selected from GWAS data from SSA

Bongani Mayosi: *'Lift as you rise …'*


Clair, MSc.


Amber, MSc.


Robyn, MSc.


Amy, MSc.

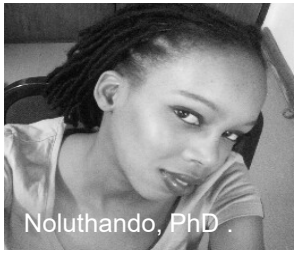

Nomlindo, MBChB


Cedrik, MD, MMed


Khuthala, PhD.


Tshepiso , MSc.


Kathryn, MSc


Noluthando, PhD .


Jean-Jacques, MD, UY1


Valentina, PhD, UY1

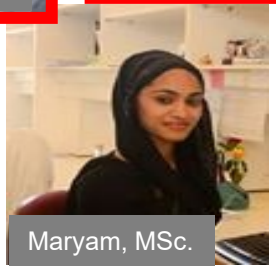

Chantelle, MSc.


Samuel, PhD, UG


Kamogelo, PhD


Gift Dineo, PhD


Jason, PhD


Maryam, MSc.


Elvis, PhD


Edmond, MD, PhD


Abdoulaye, MD, PhD

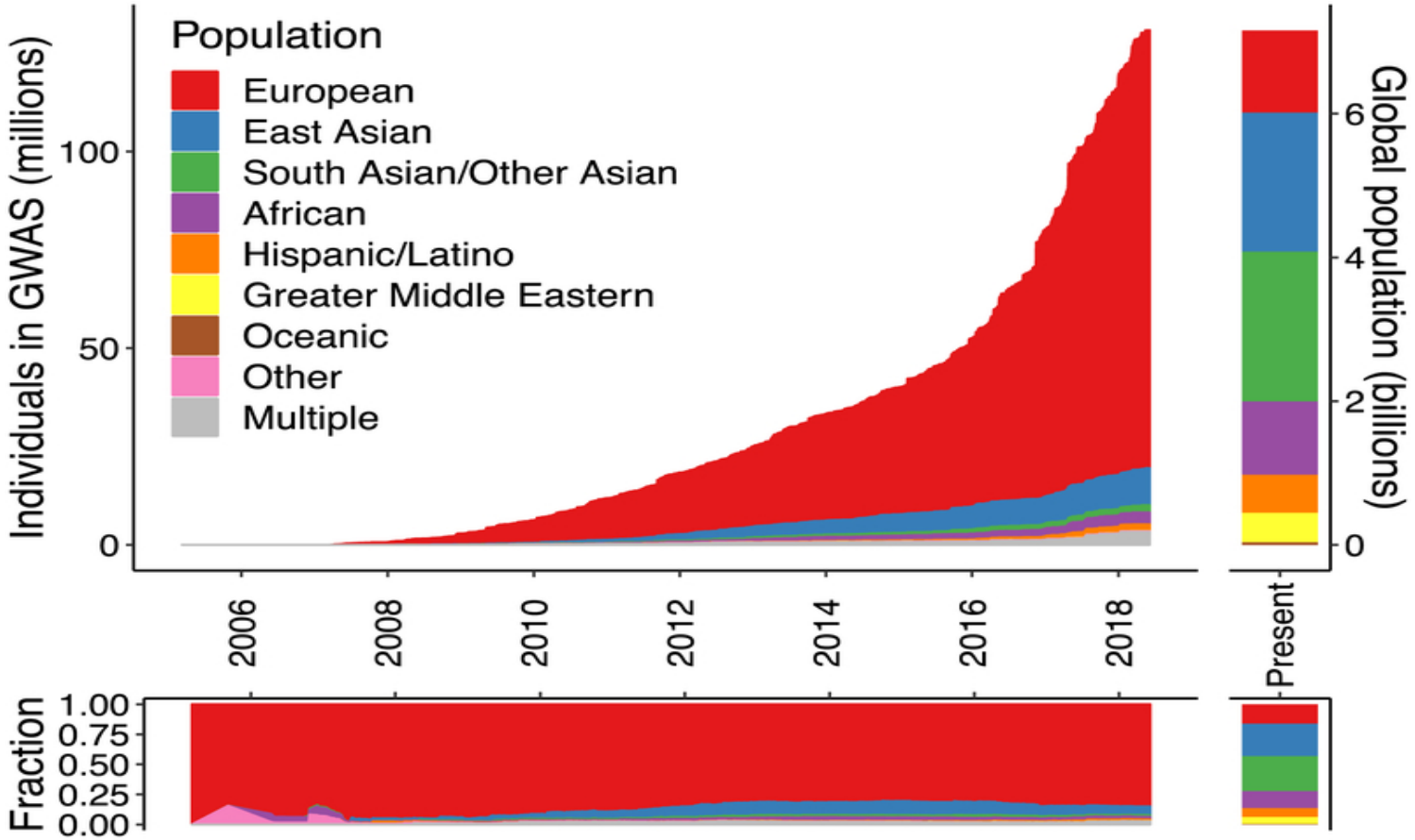

Karen, MD, PhD


Ayman, MD, MMed


Malick, MD, PhD

African Ancestry and complex traits/diseases

Only 2.5% Africans in Global GWAS Participants



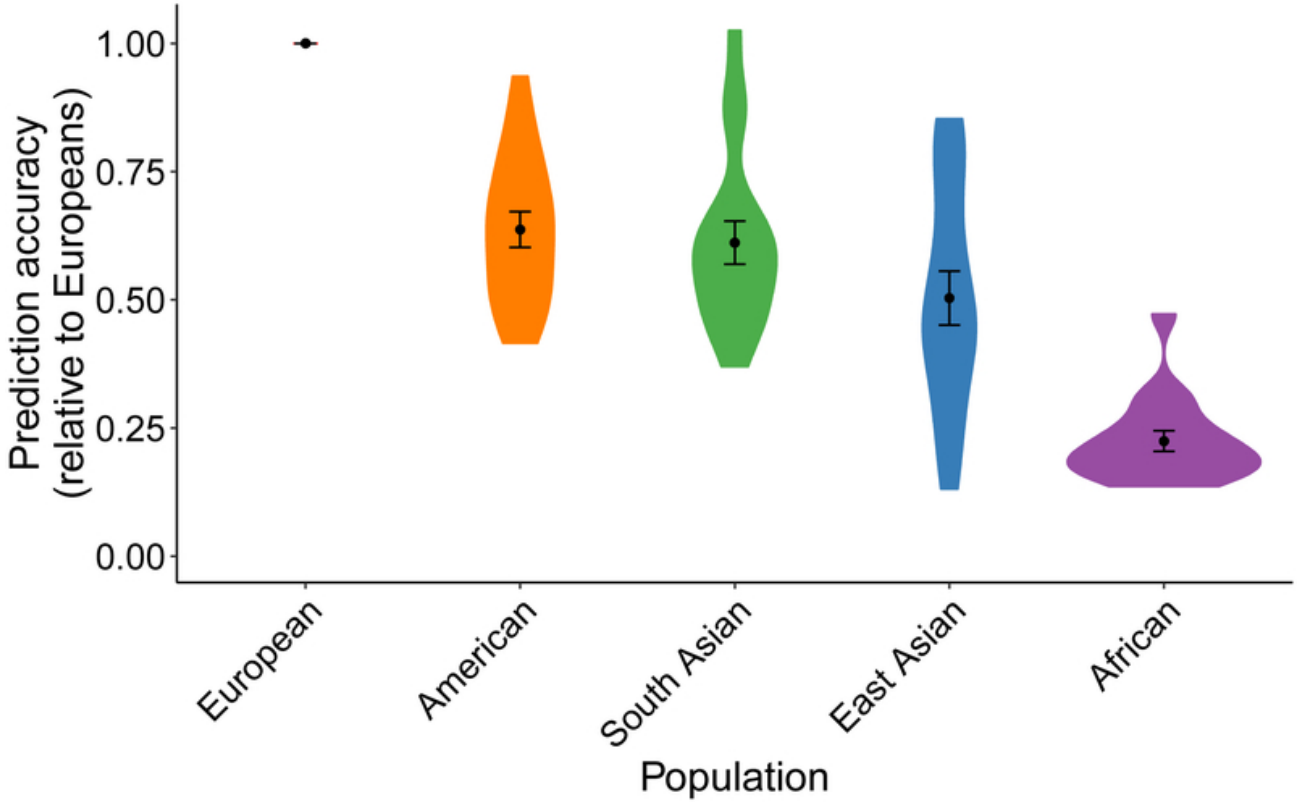
Ancestry of GWAS participants over time compared to the global population

Amrtin et al. Nat Genet . 2019 April ; 51(4): 584–591.

Dikilitas et al. AJHG 2020, 106: 707-716

Lambert et al, Hum Mol Genet, 2019, 28: R133–R142

Underperformance of PRS in Africans



Prediction accuracy relative to European ancestry individuals across 17 quantitative traits and 5 continental populations in UKBB

Amrtin et al. Nat Genet . 2019 April ; 51(4): 584–591.

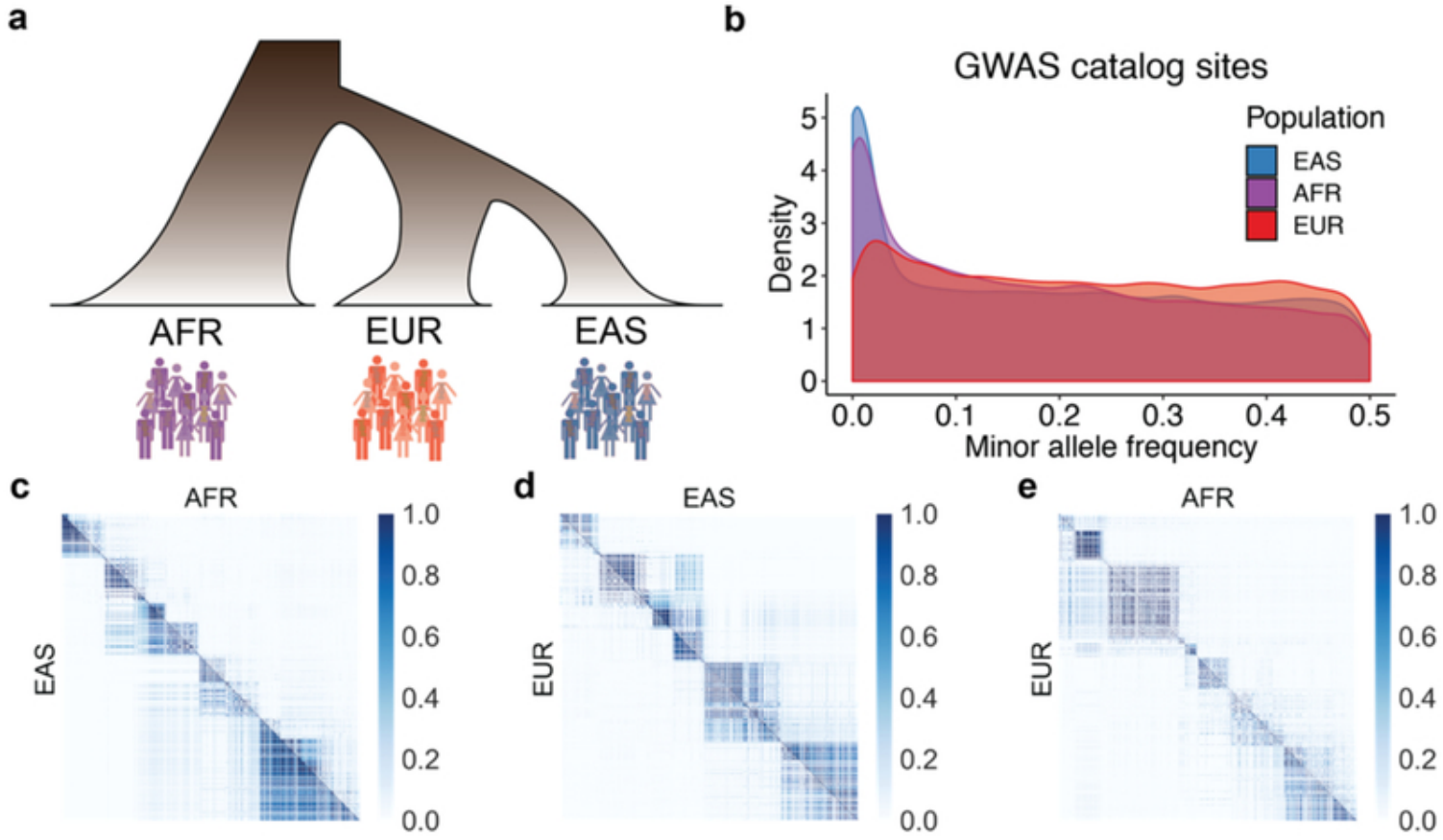
Investigations of Kidney Dysfunction-Related Gene Variants in Sickle Cell Disease Patients in Cameroon (Sub-Saharan Africa)

Valentina J. Ngo-Bitoungui[1,2,3], Suzanne Belinga[4], Khuthala Mnika[2], Tshepiso Masekoameng[2], Victoria Nembaware[1], René G. Essomba[5,6], Francoise Ngo-Sack[7], Gordon Awandare[1], Gaston K. Mazandu[2,8] and Ambroise Wonkam[2]

Front Genet. 2021; 12: 595702.

Lower LD in Africans Improve fine Mapping

Only 2.5% in GWAS studies are Africans but account for 7% of associations



Gurdasani, D. *et al. Cell* **179**, 984-1002.e36, (2019).

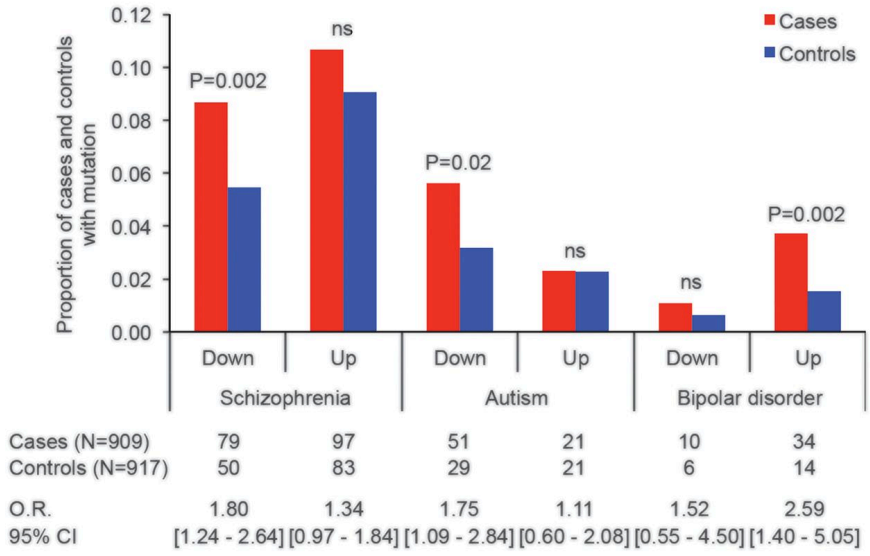
Gurdasani, D. *et al. Nat Rev Genet* **20**, 520-535, (2019).

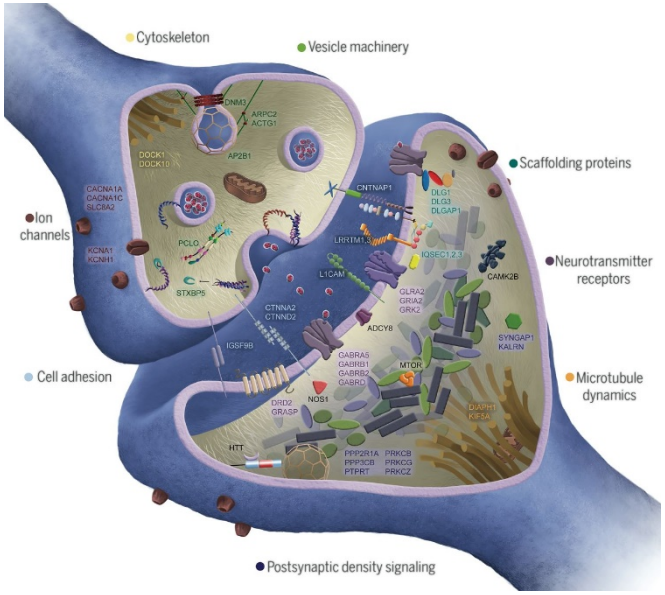
Amrtin et al. Nat Genet . 2019 April ; 51(4): 584–591.

Lower Africans Samples Size Yields Larger Effect Sizes

Genetics of schizophrenia in the South African Xhosa

S. Gulsuner[1], D. J. Stein[2], E. S. Susser[3,4], G. Sibeko[2], A. Pretorius[2], T. Walsh[1], L. Majara[5],



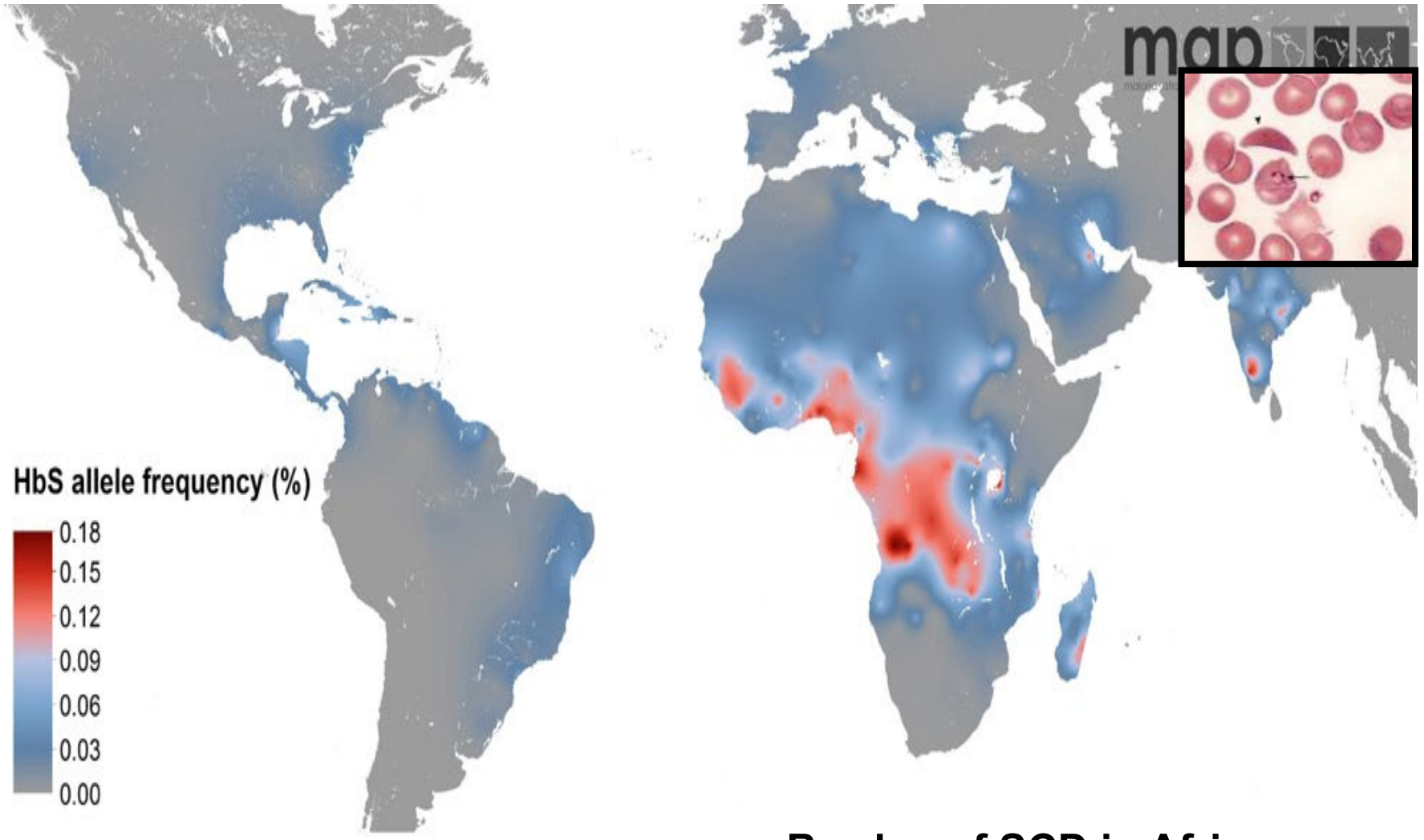


- Rare damaging mutations in multiple genes in ~ 1000 African
- Replicated in a Swedish cohort of 5000 cases.
- Africans yielded larger effect sizes

Gulsuner *et al.*, *Science* 367, 569–573 (2020)

Sickle Cell Disease:
The Tragedy of the Common(s)…

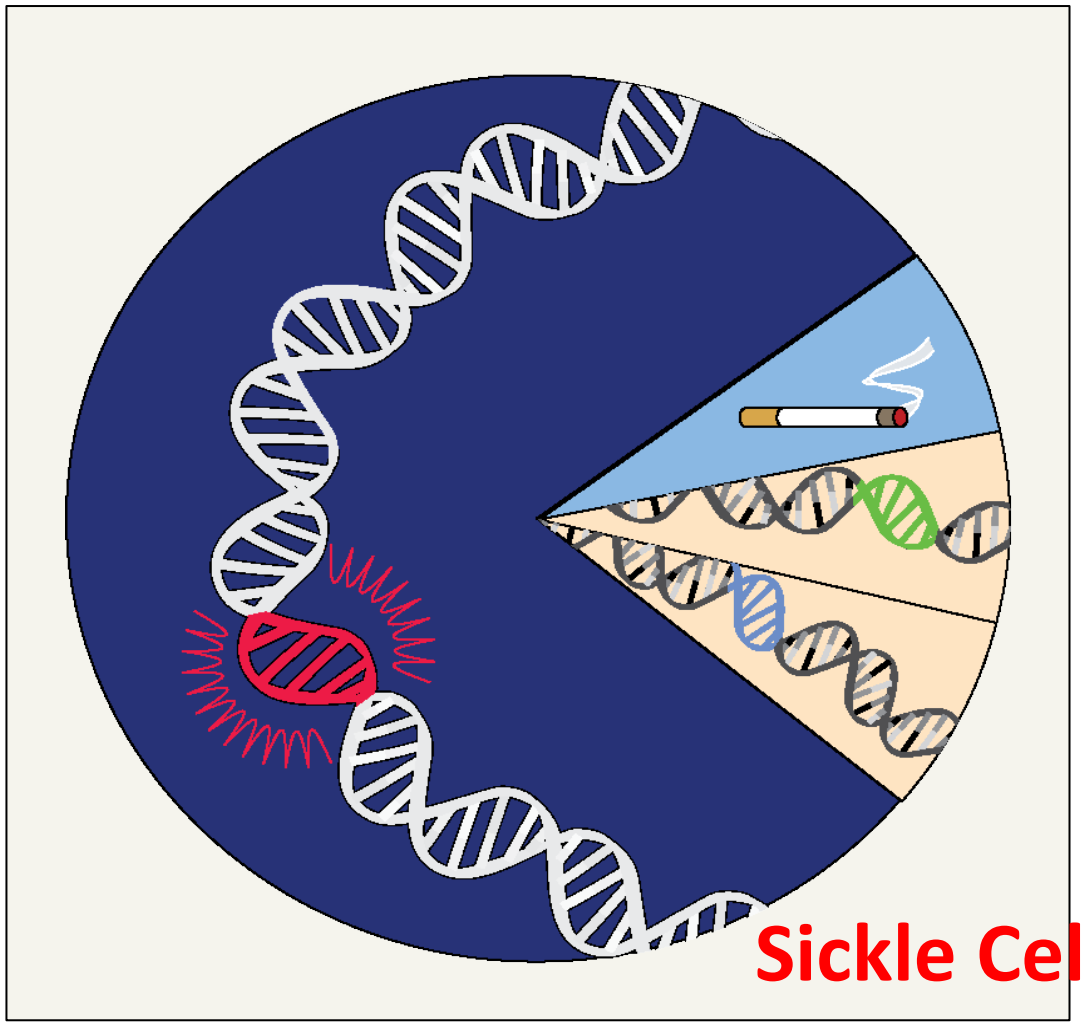
Global Burden of SCD



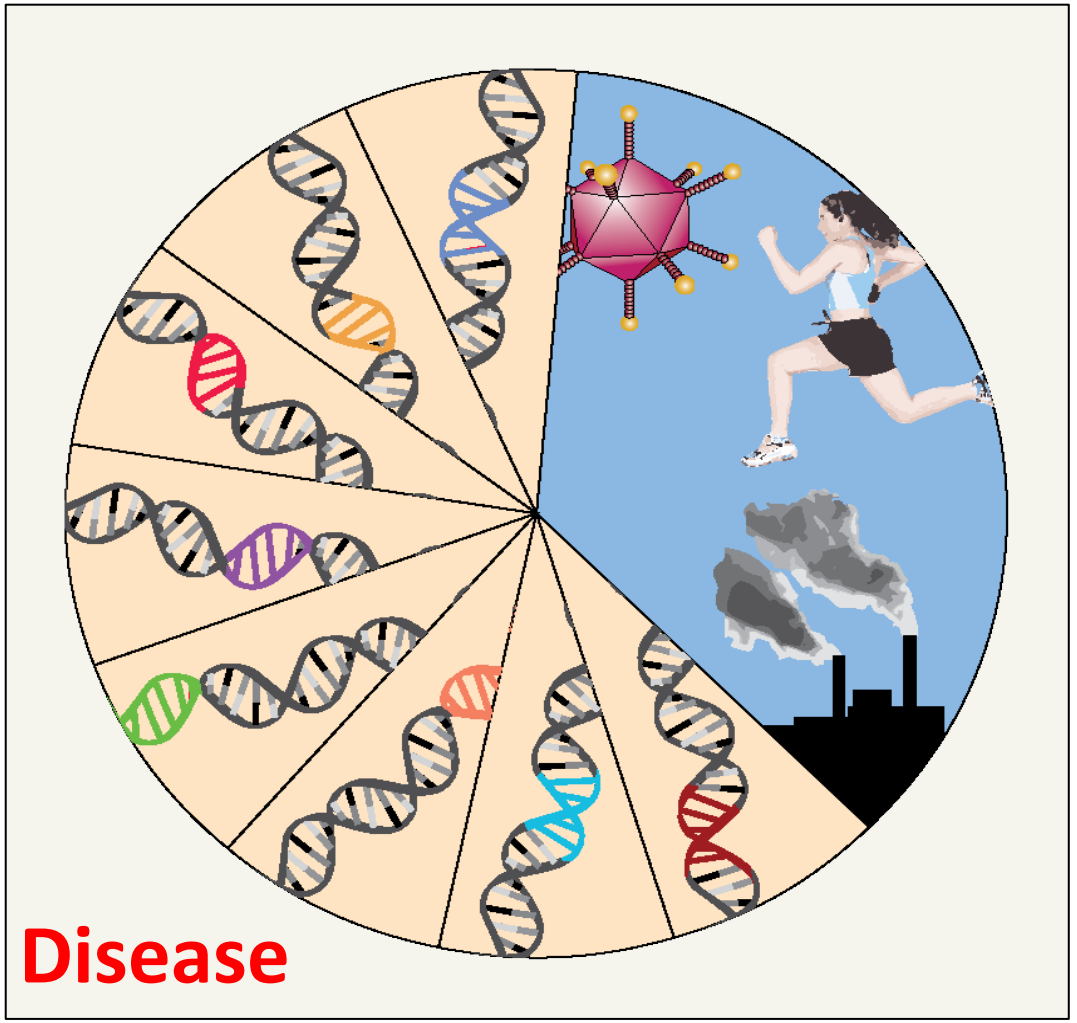
Burden of SCD in Africa
237, 253 births a year (76%)

Piel et al, The Lancet, 2013

Genomic Architecture of Genetic Diseases



Sickle Cell Disease



Rare, Simple, Monogenic, Mendelian…

Common, Complex, Multigenic, Non-Mendelian…

Genetic and Kidney dysfunctions in SCD

bjh research paper

Clinical and genetic predictors of renal dysfunctions in sickle cell anaemia in Cameroon

Amy Geard,[1] Gift D. Pule,[1] Bernard Chetcha Chemegni,[2] Valentina J. Ngo Bitoungui,[2] Andre P. Kengne,[3] Emile R. Chimusa[1] and Ambroise Wonkam[1]

Summary

Micro-albuminuria and glomerular hyperfiltration are primary indicators of renal dysfunctions in Sickle Cell Disease (SCD), with more severe manifes-

OPEN ACCESS Freely available online

PLOS ONE

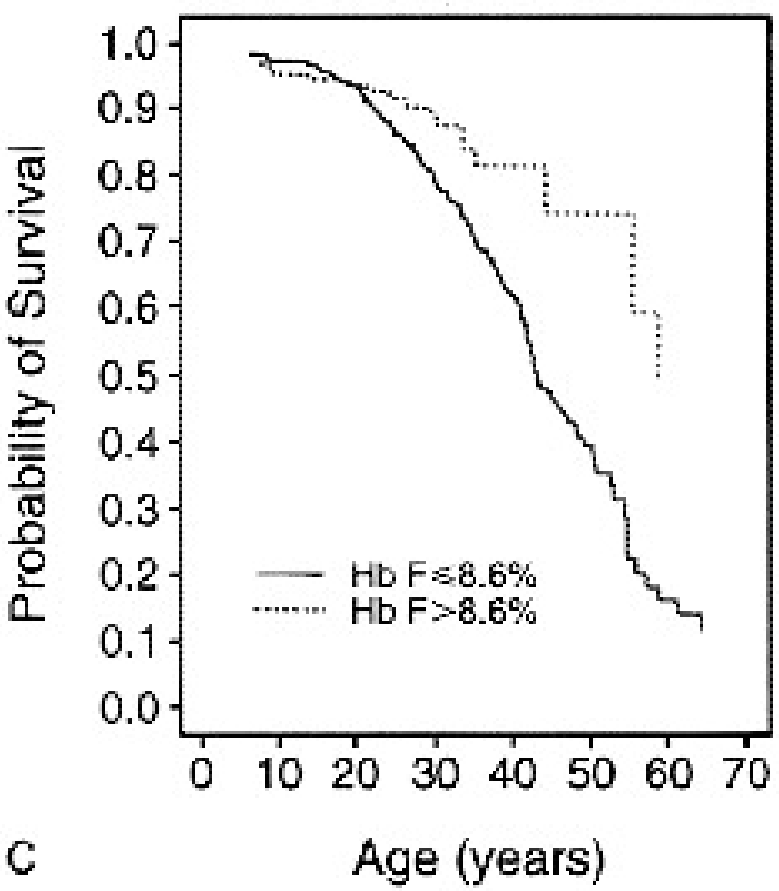
The Co-Inheritance of Alpha-Thalassemia and Sickle Cell Anemia Is Associated with Better Hematological Indices and Lower Consultations Rate in Cameroonian Patients and Could Improve Their Survival

Maryam Bibi Rumaney[1], Valentina Josiane Ngo Bitoungui[2], Anna Alvera Vorster[1], Raj Ramesar[1,3], Andre Pascal Kengne[4], Jeanne Ngogang[2], Ambroise Wonkam[1]*

Investigations of Kidney Dysfunction-Related Gene Variants in Sickle Cell Disease Patients in Cameroon (Sub-Saharan Africa)

*Valentina J. Ngo-Bitoungui[1,2,3], Suzanne Belinga[4], Khuthala Mnika[2], Tshepiso Masekoameng[2], Victoria Nembaware[1], René G. Essomba[5,6], Francoise Ngo-Sack[7], Gordon Awandare[1], Gaston K. Mazandu[2,8] and Ambroise Wonkam[2]**

SCD, and HbF, and survival



C

N Engl J Med 1994;330:1639-44.

DNA polymorphisms at the *BCL11A*, *HBS1L-MYB*, and *β-globin* loci associate with fetal hemoglobin levels and pain crises in sickle cell disease

Guillaume Lettre*†‡§, Vijay G. Sankaran‡¶, Marcos André C. Bezerra**, Aderson S. Araújo**, Manuela Uda††, Serena Sanna††, Antonio Cao††, David Schlessinger‡‡, Fernando F. Costa§§, Joel N. Hirschhorn*†§, and Stuart H. Orkin§¶

blood

2011 117: 1390-1392
Prepublished online November 10, 2010;
doi:10.1182/blood-2010-08-302703

Genetics of fetal hemoglobin in Tanzanian and British patients with sickle cell anemia

Julie Makani, Stephan Menzel, Siana Nkya, Sharon E. Cox, Emma Drasar, Deogratius Soka, Albert N. Komba, Josephine Mgaya, Helen Rooks, Nisha Vasavda, Gregory Fegan, Charles R. Newton, Martin Farrall and Swee Lay Thein

OPEN ACCESS Freely available online

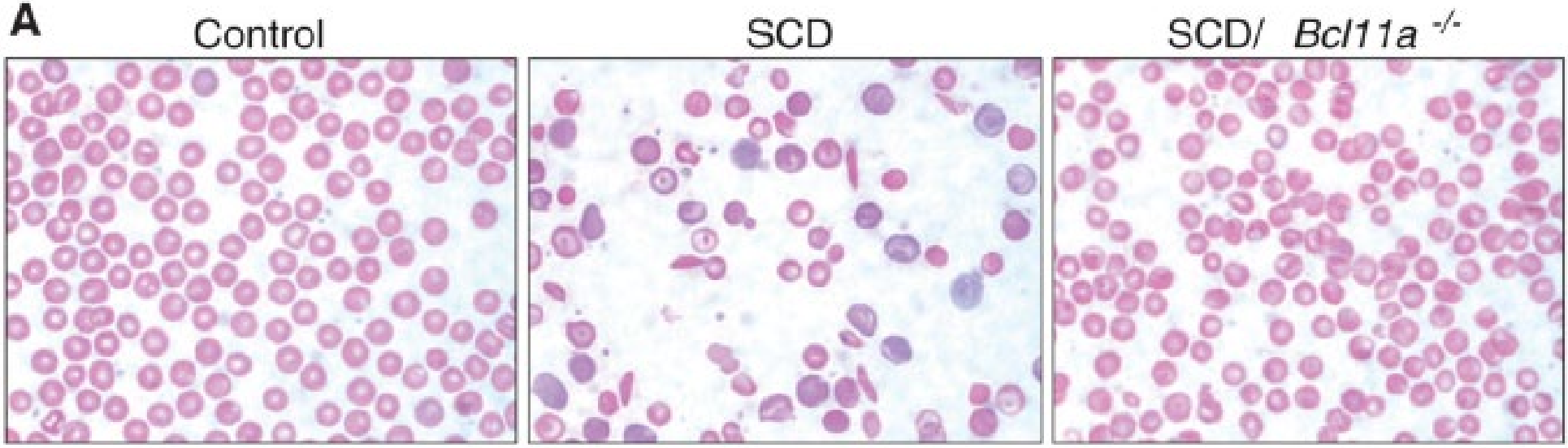
PLOS | ONE

Association of Variants at *BCL11A* and *HBS1L-MYB* with Hemoglobin F and Hospitalization Rates among Sickle Cell Patients in Cameroon

Ambroise Wonkam[1*], Valentina J. Ngo Bitoungui[2], Anna A. Vorster[1], Raj Ramesar[1,3], Richard S. Cooper[4], Bamidele Tayo[4], Guillaume Lettre[5], Jeanne Ngogang[2]

Correction of Sickle Cell Disease Adult Mice by Interference with Fetal Hemoglobin Silencing

Jian Xu,[1,2] Cong Peng,[1*] Vijay G. Sankaran,[1,5*] Zhen Shao,[1] Erica B. Esrick,[1,3] Bryan G. Gregory C. Ippolito,[4] Yuko Fujiwara,[1,2] Benjamin L. Ebert,[3] Philip W. Tucker,[4] Stuart H.



BCL11A enhancer dissection by Cas9–mediated *in situ* saturating mutagenesis

Matthew C. Canver[1*], Elenoe C. Smith[1*], Falak Sher[1*], Luca Pinello[2*], Neville E. Sanjana[3*], Ophir Shalem[3], Diane D. Chen[1], Patrick G. Schupp[1], Divya S. Vinjamur[1], Sara P. Garcia[2], Sidinh Luc[1], Ryo Kurita[4], Yukio Nakamura[4,5], Yuko Fujiwara[1,6], Takahiro Maeda[7], Guo-Cheng Yuan[2], Feng Zhang[3§], Stuart H. Orkin[1,6§] & Daniel E. Bauer[1§]

It's Here: Gene Editing for SCD

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Gene Therapy in a Patient with Sickle Cell Disease

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia

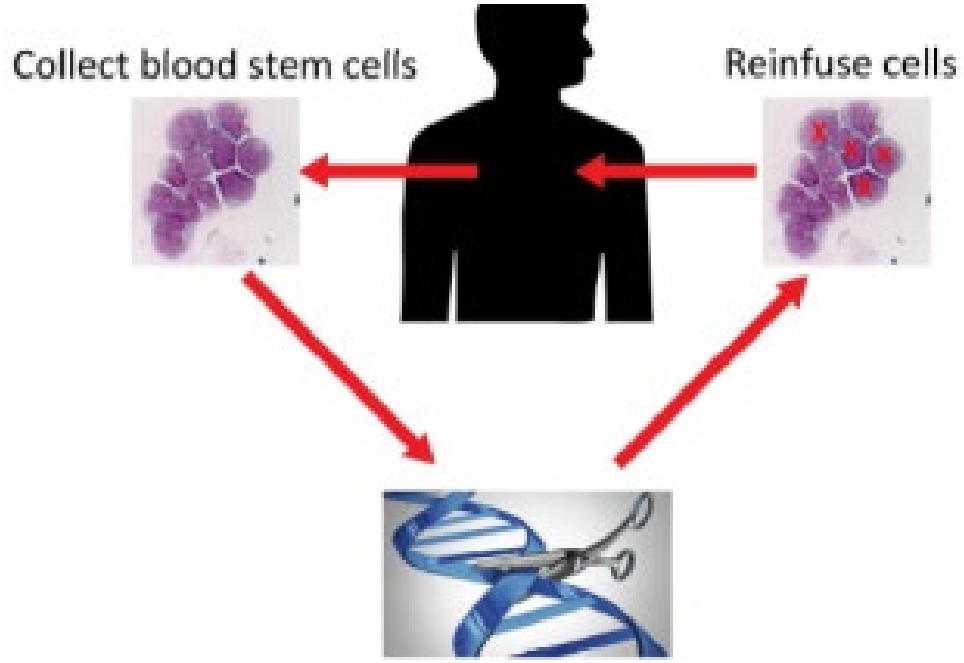
H. Frangoul, D. Altshuler, M.D. Cappellini, Y.-S. Chen, J. Domm, B.K. Eustace,

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 21, 2021 VOL. 384 NO. 3

Post-Transcriptional Genetic Silencing of *BCL11A* to Treat Sickle Cell Disease

Erica B. Esrick, M.D., Leslie E. Lehmann, M.D., Alessandra Biffi, M.D., Ph.D., Maureen Achebe, M.D.,

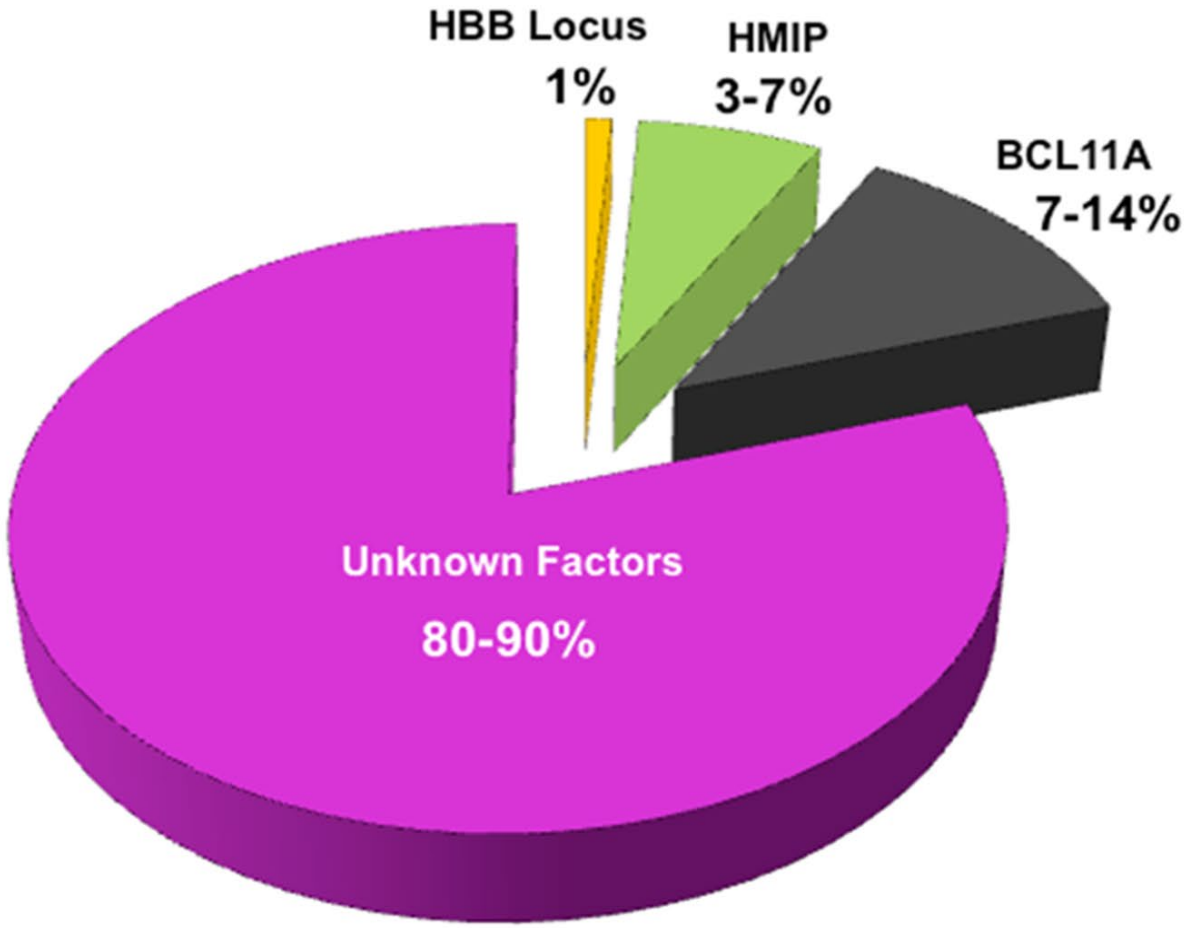


N ENGL J MED 376;9 NEJM.ORG MARCH 2, 2017

N Engl J Med 2021;384:252-60.

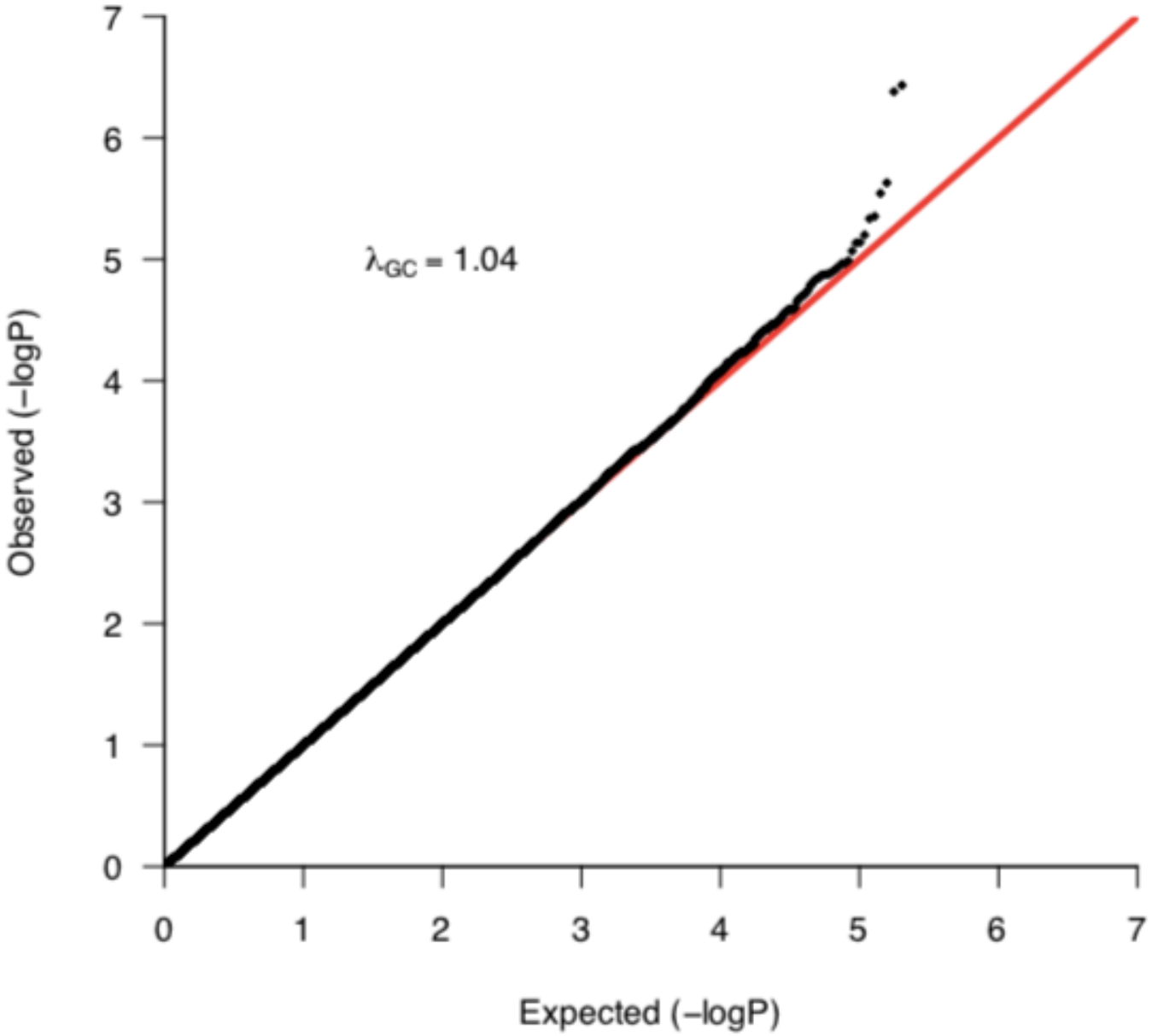
N ENGL J MED 384;3 NEJM.ORG JANUARY 21, 2021

Missing Heritability of HbF in Africa



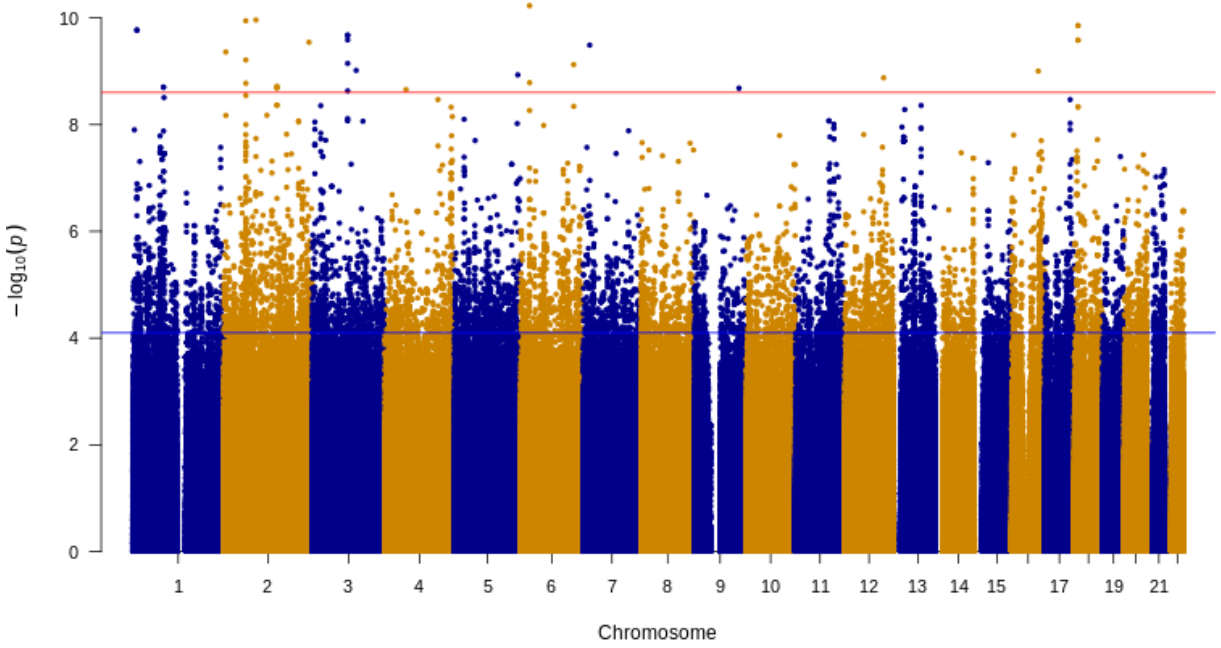
Wonkam, *Br J Haematol.* 2020 Dec;191(5):668-670.

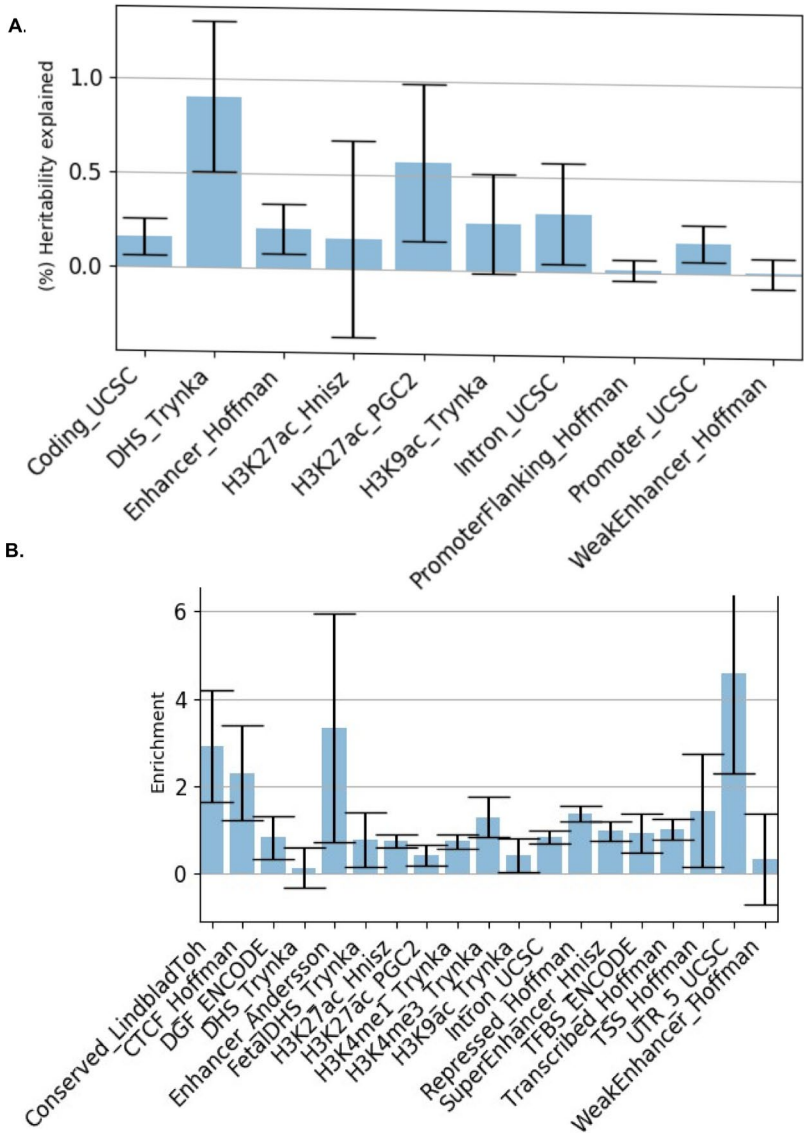
Genomics of Hb F level in SCA



Wonkam et al, Unpublished data

Novel HbF Promoting Loci in Africans





Wonkam et al, Unpublished data

NEWS FEATURE · 04 DECEMBER 2019

Gene therapy is facing its biggest challenge yet

After finally gaining traction as a potential treatment for certain genetic disorders, gene therapy tackles the challenge of sickle-cell disease.

Heidi Ledford

Hydroxyurea-Induced miRNA & HbF

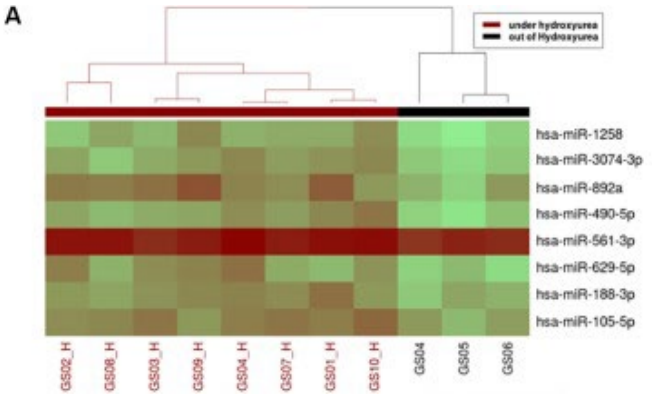
EXPERT REVIEWS

A systematic review of known mechanisms of hydroxyurea-induced fetal hemoglobin for treatment of sickle cell disease

Expert Rev. Hematol. Early online, 1–11 (2015)

Gift D Pule[1], Shaheen Mowla[2], Nicolas Novitzky[2], Charles S Wiysonge[3] and Ambroise Wonkam*[1]

Aim: To report on molecular mechanisms of fetal hemoglobin (HbF) induction by hydroxyurea (HU) for the treatment of sickle cell disease. Study Design: Systematic review. Results: Studies have provided consistent associations between genomic variations in HbF-promoting loci and variable HbF level in response to HU. Numerous signal transduction pathways have been implicated, through the identification of key genomic variants in *BCL11A*, *HBS1L-MYB*, *SAR1* or *XmnI* polymorphism that predispose the response to the treatment, and signal transduction pathways that modulate γ-globin expression (cAMP/cGMP; Gi/o/c-Jun N-terminal kinase/Jun;



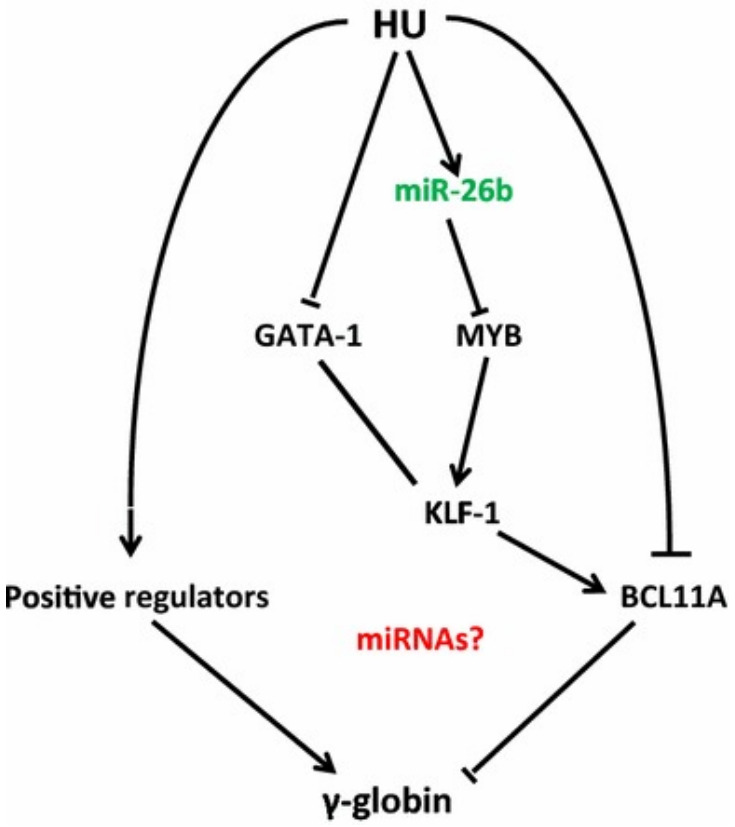
Pule *et al. Clin Trans Med* (2016) 5:15
DOI 10.1186/s40169-016-0092-7

Clinical and Translational Medicine

RESEARCH Open Access

Hydroxyurea down-regulates *BCL11A*, *KLF-1* and *MYB* through miRNA-mediated actions to induce γ-globin expression: implications for new therapeutic approaches of sickle cell disease

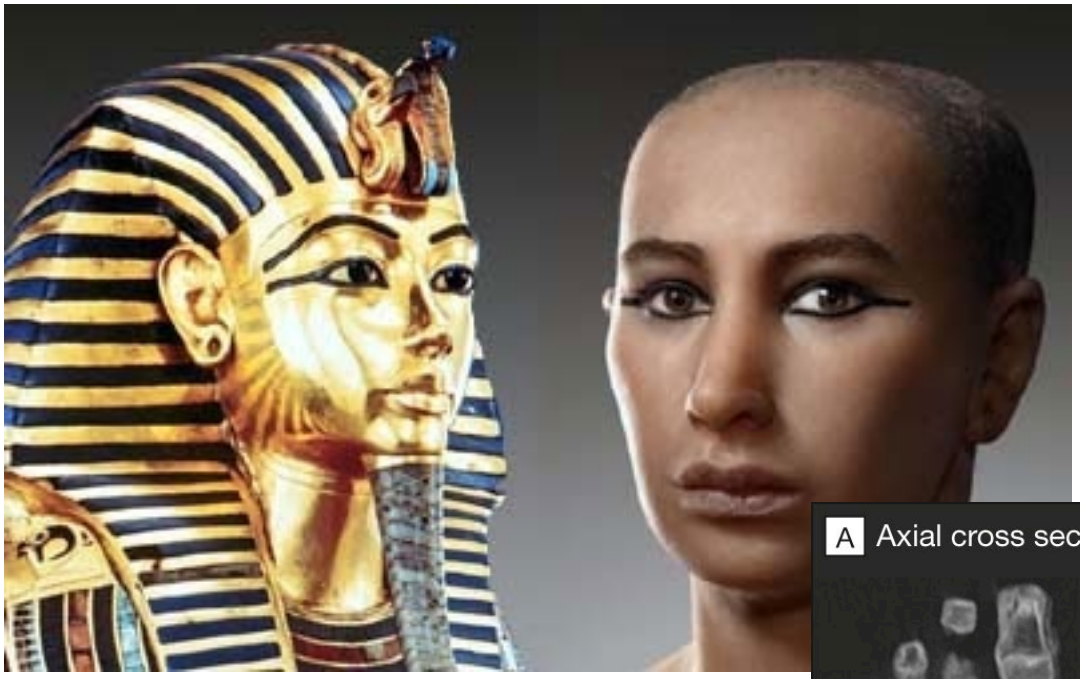
Gift Dineo Pule[1], Shaheen Mowla[2], Nicolas Novitzky[2] and Ambroise Wonkam[1*]

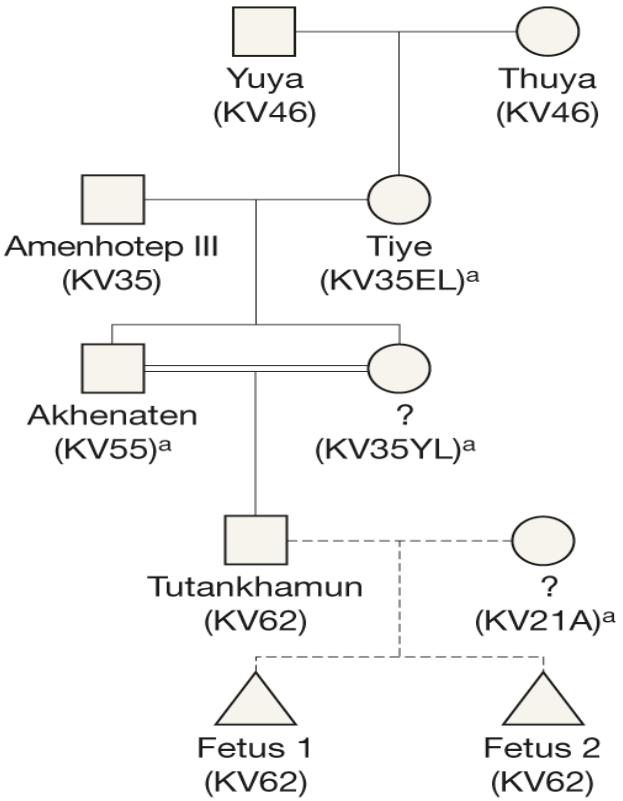


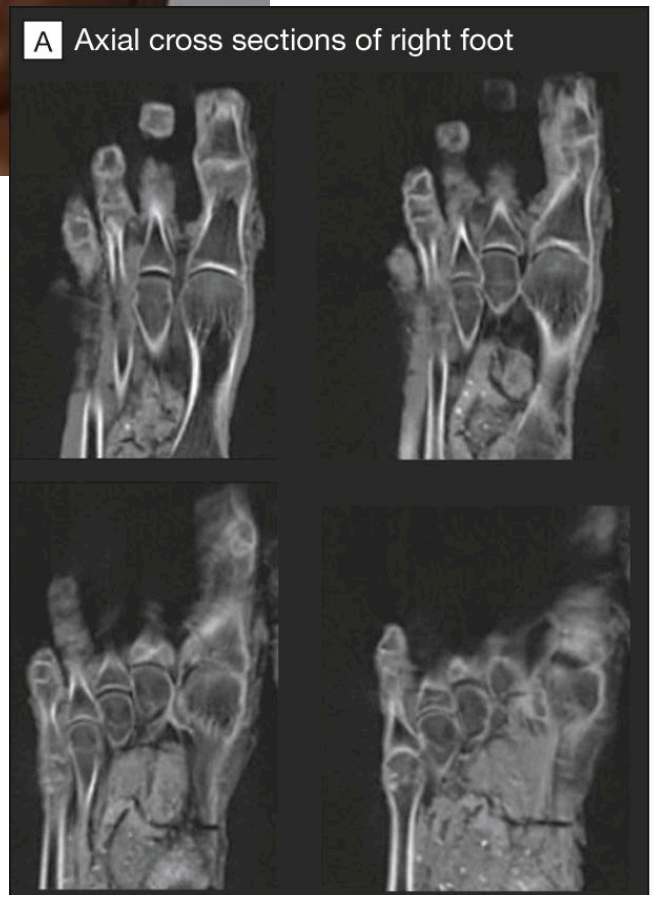
Hydroxyurea-Induced miRNA Expression in Sickle Cell Disease Patients in Africa

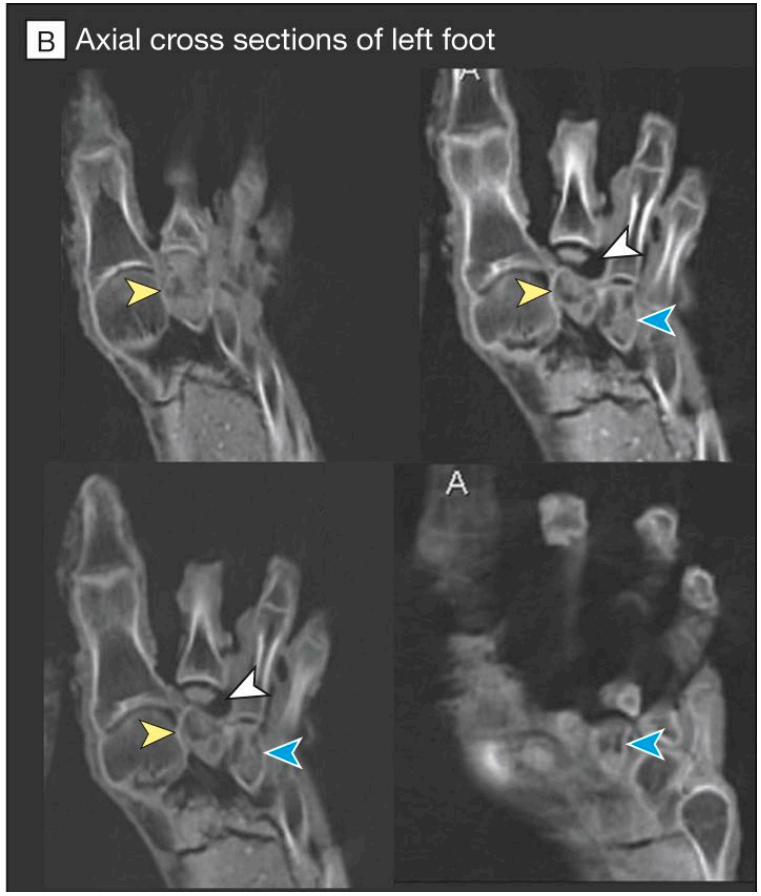
*Khuthala Mnika[1], Gaston K. Mazandu[1,2], Mario Jonas[1], Gift D. Pule[1], Emile R. Chimusa[1], Neil A. Hanchard[3] and Ambroise Wonkam[1]**

Tutankhamun had Sickle Cell Disease?





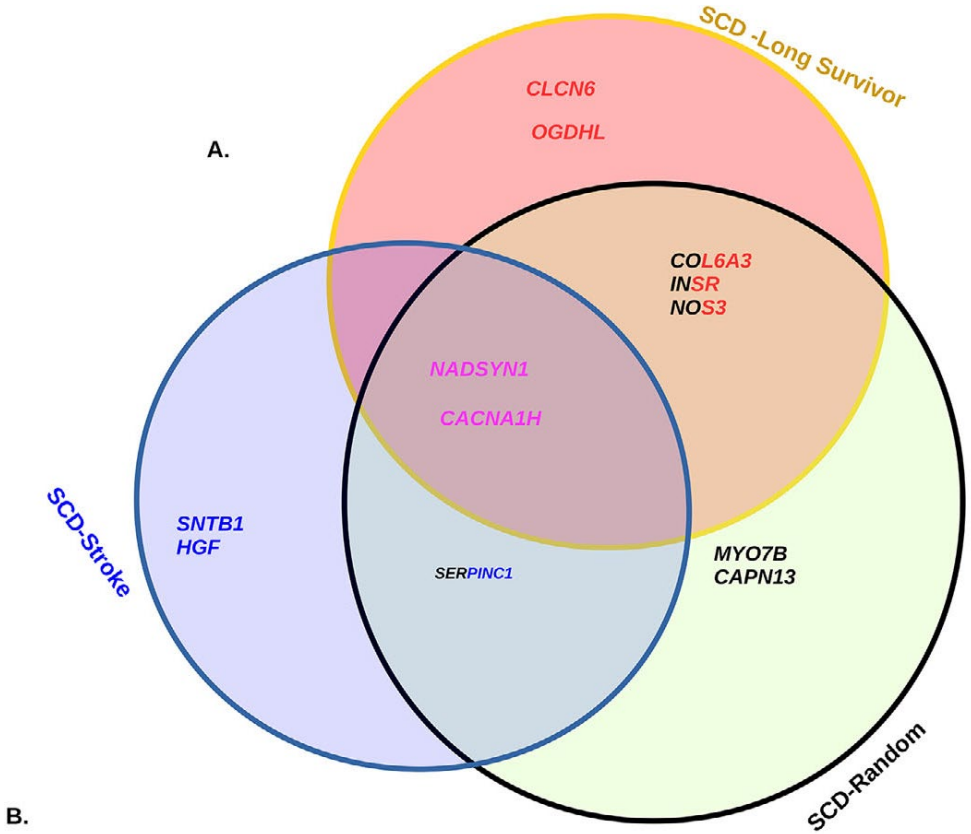


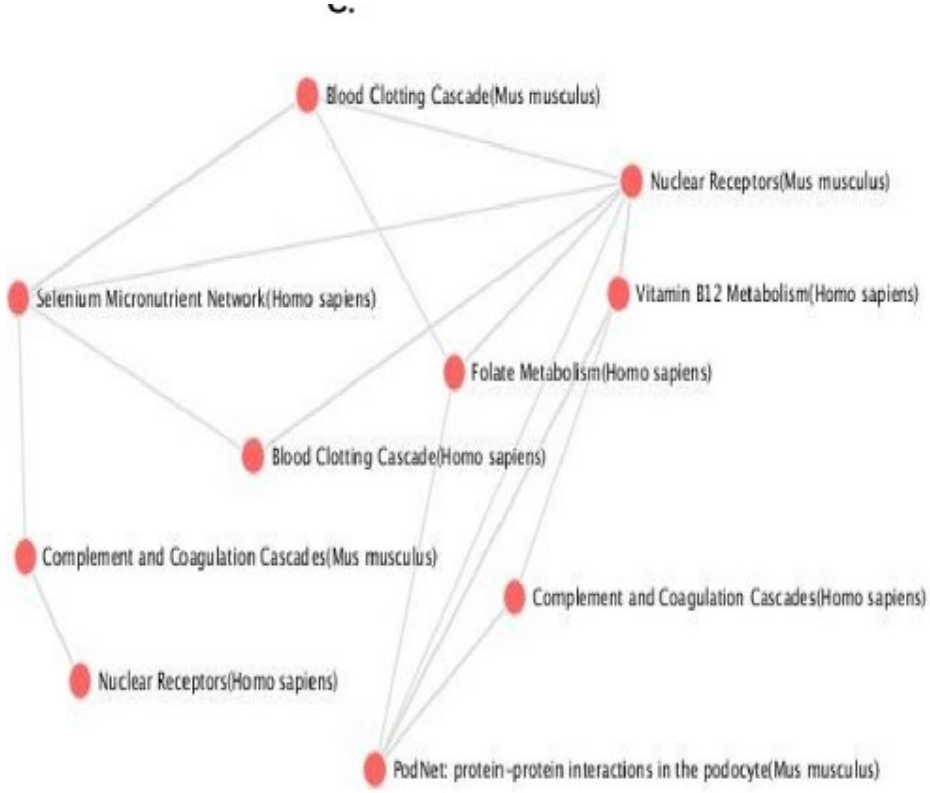


Hawass *et al. JAMA*. 2010 Feb 17;303(7):638-47.

Timmann & Meyer JAMA. 2010 Jun 23;303(24):2473

Rare Damaging Variants & Survival in SCD





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DOI: 10.1002/ctm2.152

RESEARCH ARTICLE

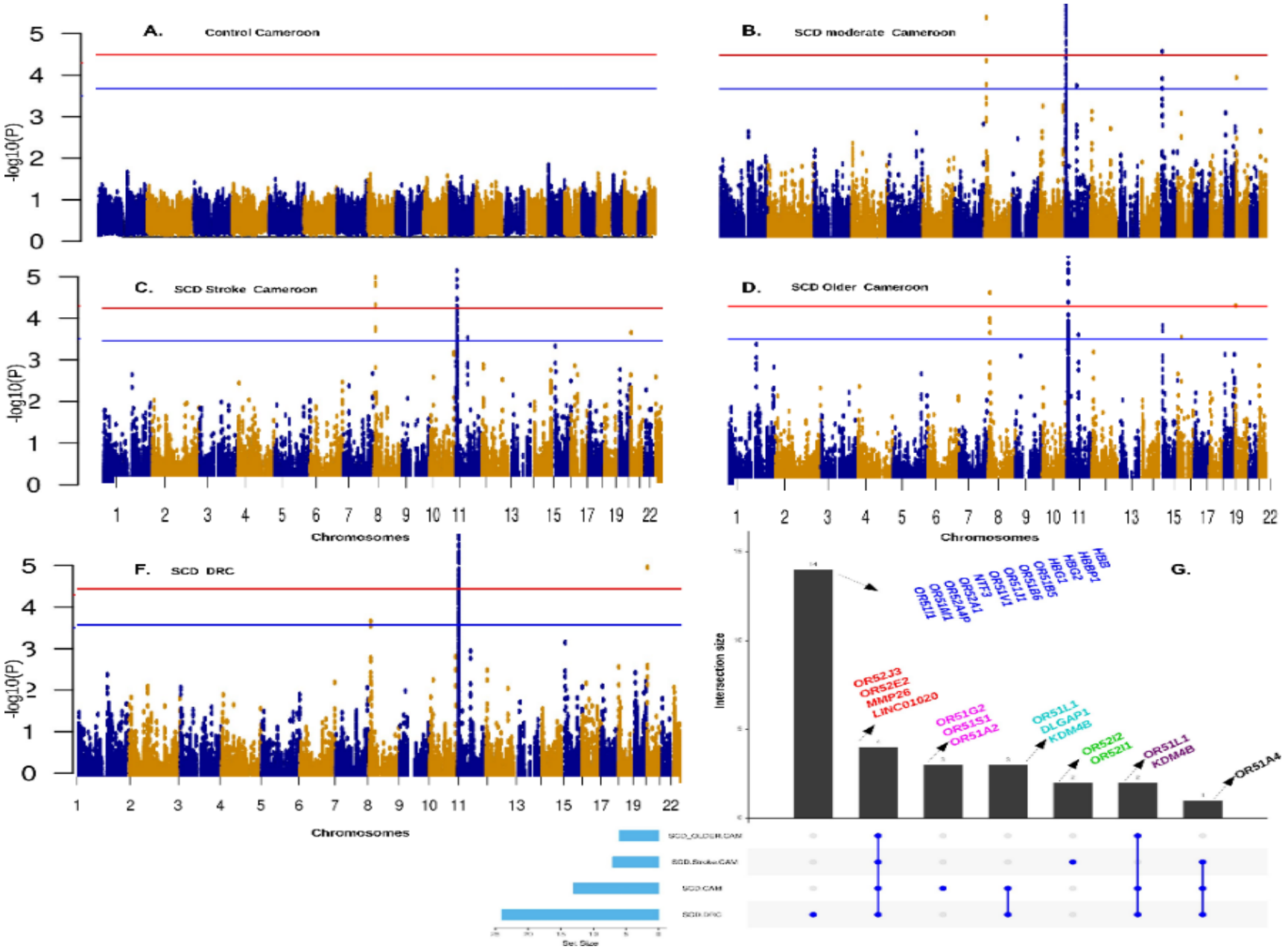
CLINICAL AND TRANSLATIONAL MEDICINE

WILEY

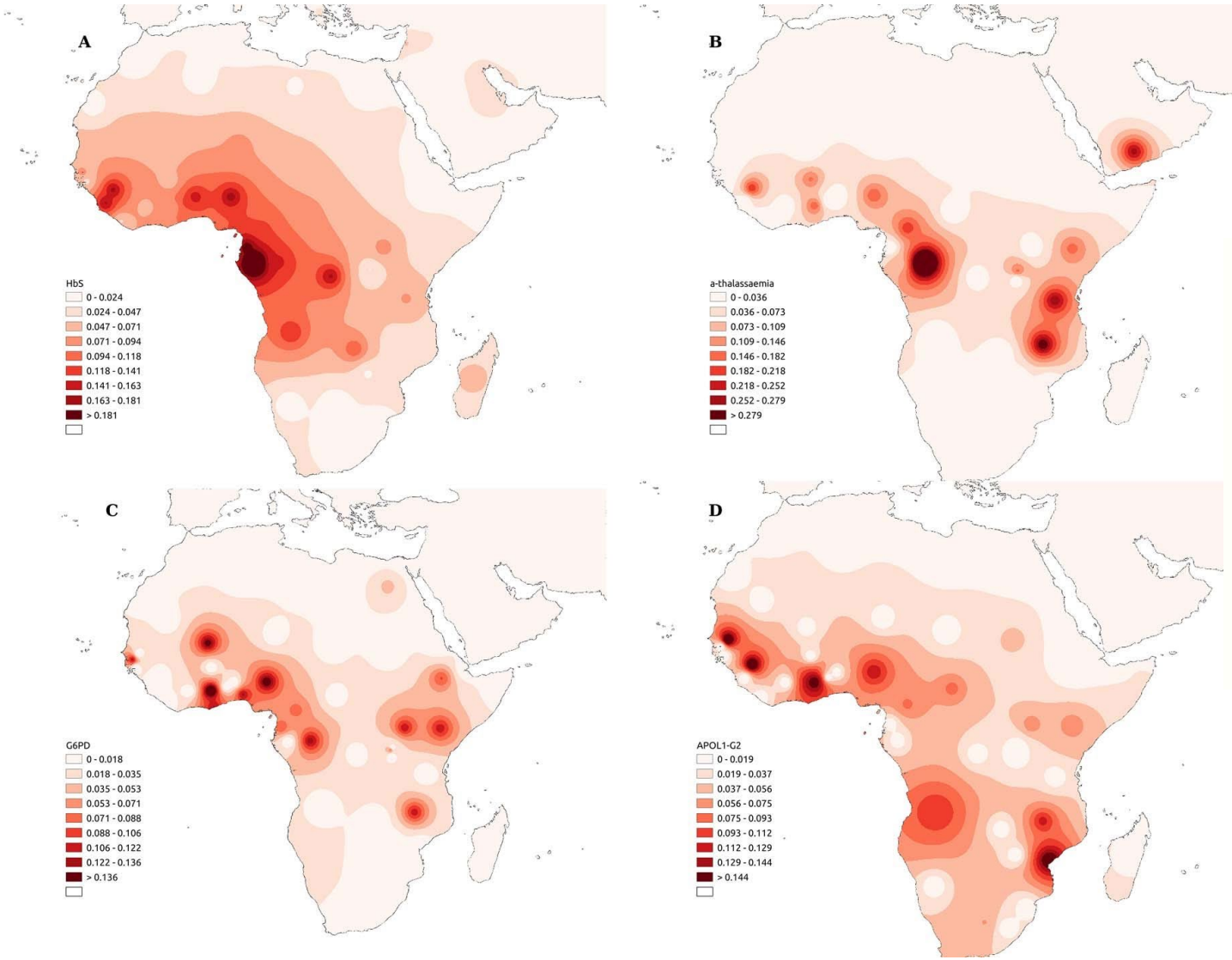
Genetic modifiers of long-term survival in sickle cell anemia

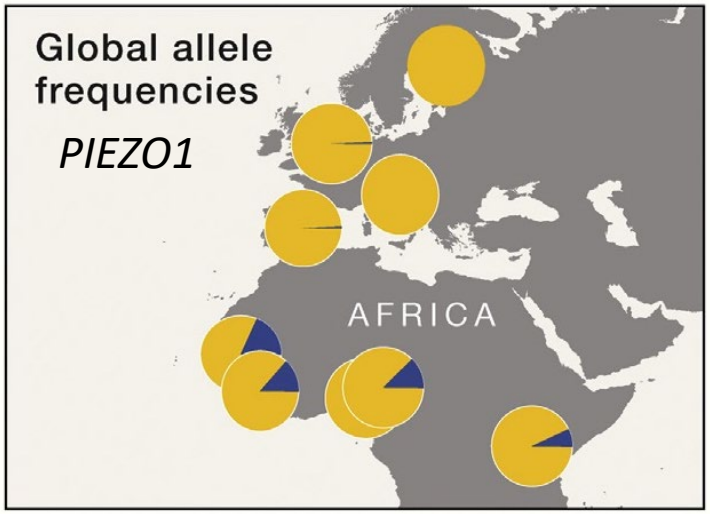
Ambroise Wonkam[1,2] | Emile R. Chimusa[1,2] | Khuthala Mnika[1] | Gift Dineo Pule[1] | Valentina Josiane Ngo Bitoungui[1] | Nicola Mulder[3] | Daniel Shriner[4] | Charles N. Rotimi[4] | Adebowale Adeyemo[4]

Markers of evolutional selections in SCD



Co-evolution of *HBB*-β^S and other variants under selection





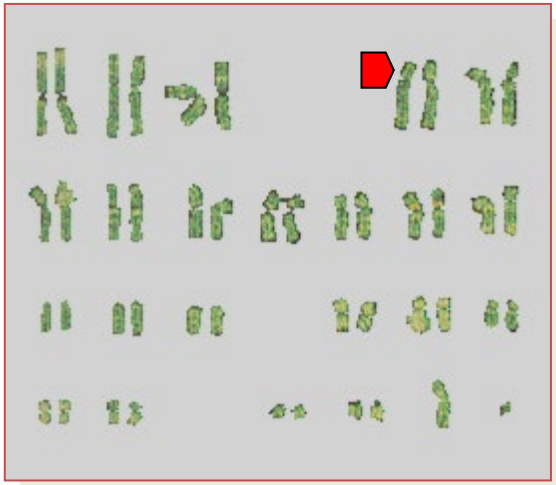
Esoh & Wonkam, *Hum Mol. Genet.* https://doi.org/10.1093/hmg/ddab004, 18 January 2021

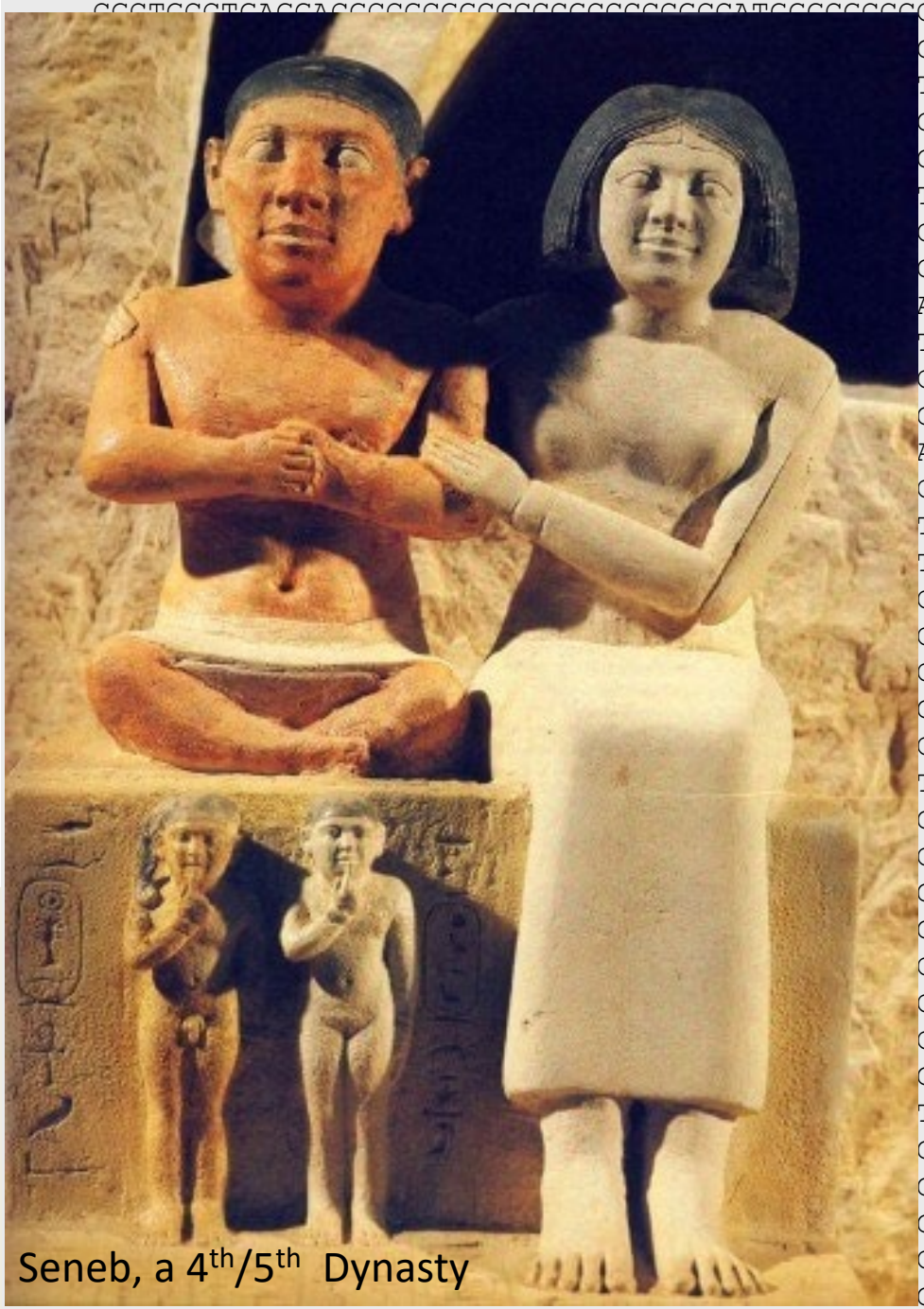
Hanchard & Wonkam, Cell *184*, February 18, 2021

The tragedy of the rare: DSDs

Achondroplasia

FGFR3 gene





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TGGTGCAGCTGCCAGCCGAGG
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TCAAGCTGCTGAAGGAGGGCC
GCGGGAGTGCTGGCATGCCGC
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GCCAGGACACCCCCAGCTCCA
CCCACCCAGCAGTGGGGGCTC
GCCCTCCCTGCTGCTGG....

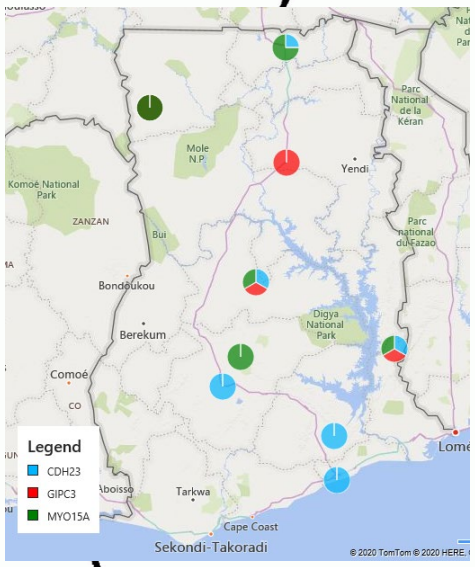
Unknown in the Databases:

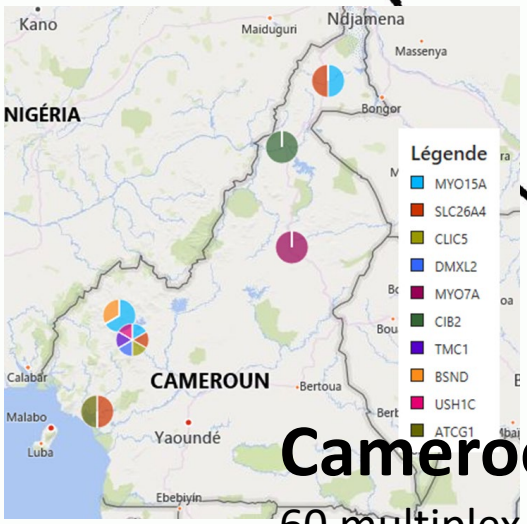
The case of a silent epidemy

HI Genes Africa
WES analysis

Ghana

54 multiplex families
200 single plex
92% resolution rate
GJB2-R143W: 33%

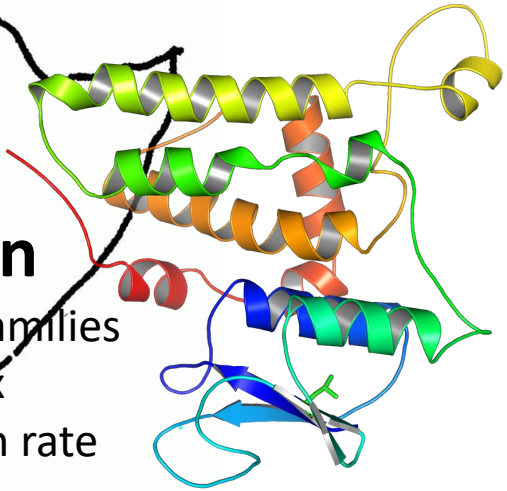


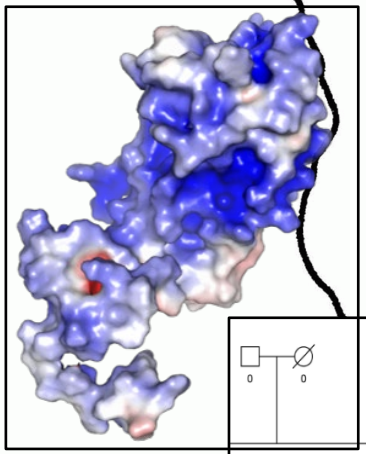


Cameroon

60 multiplex families
400 single plex
61% resolution rate
Novel genes:

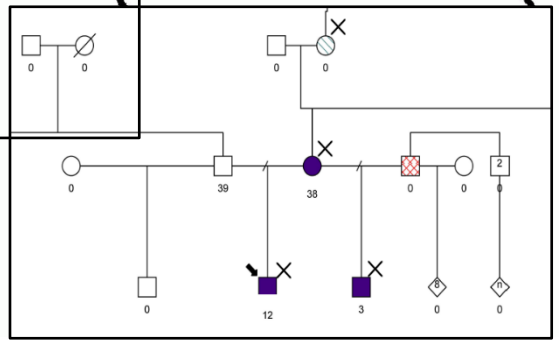
***CLIC5*: c.224T>C (p.L75P) / c.63+1G>A**





South Africa

50 multiplex families
250 single plex
70% resolution rate
Higher Autosomal dominant
Novel genes: *REST*



Confirmation of Rare Disease Genes in Africa

A novel variant in *DXML2* gene is associated with autosomal dominant non-syndromic hearing impairment (DFNA71) in a Cameroonian family

Edmond Wonkam-Tingang[1], Isabelle Schrauwen[2], Kevin K Esoh[1], Thashi Bharadwaj[2], Liz M Nouel-Saied[2], Anushree Acharya[2], Abdul Nasir[3], Suzanne M Leal[2] and Ambroise Wonkam[1]

Bi-Allelic Novel Variants in *CLIC5* Identified in a Cameroonian Multiplex Family with Non-Syndromic Hearing Impairment

Edmond Wonkam-Tingang [1], Isabelle Schrauwen [2], Kevin K. Esoh [1], Thashi Bharadwaj [2], Liz M. Nouel-Saied [2], Anushree Acharya [2], Abdul Nasir [3], Samuel M. Adadey [1,4], Shaheen Mowla [5], Suzanne M. Leal [2] and Ambroise Wonkam [1,*]

Whole exome sequencing reveals a biallelic frameshift mutation in *GRXCR2* in hearing impairment in Cameroon

Ambroise Wonkam[1,2] | Kamogelo Lebeko[1] | Shaheen Mowla[3] | Jean Jacques Noubiap[4] | Mike Chong[5] | Guillaume Pare[5]

Whole exome sequencing identifies rare coding variants in nove human-mouse ortholog genes in African individuals diagnosed with non-syndromic hearing impairment

Oluwafemi G Oluwole[1], Kevin K Esoh[1], Edmond Wonkam-Tingang[1], Noluthando Manyisa[1], Jean Jacques Noubiap[2], Emile R Chimusa[1] and Ambroise Wonkam[1,3]

Experimental Biology and Medicine 2021; **246**: 197–206

Mol Genet Genomic Med. 2021;00:e1609.

Genes **2020**, *11*, 1249; doi:10.3390/genes11111249

***Experimental Biology and Medicine* 2021; 0: 1–9.** |

PRINT ISSN 0964-6906, ONLINE ISSN 1460-2083

HUMAN MOLECULAR GENETICS

Volume 29 Number 23 1 DECEMBER 2020

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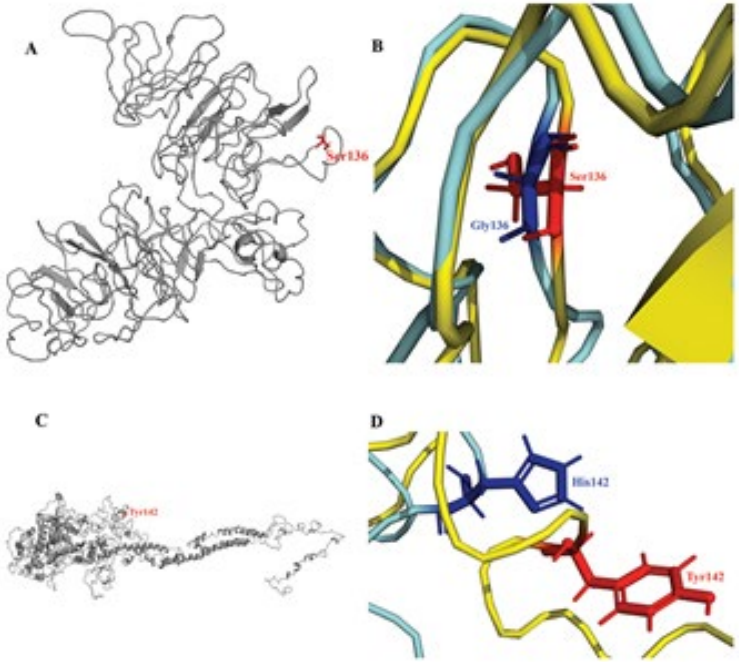
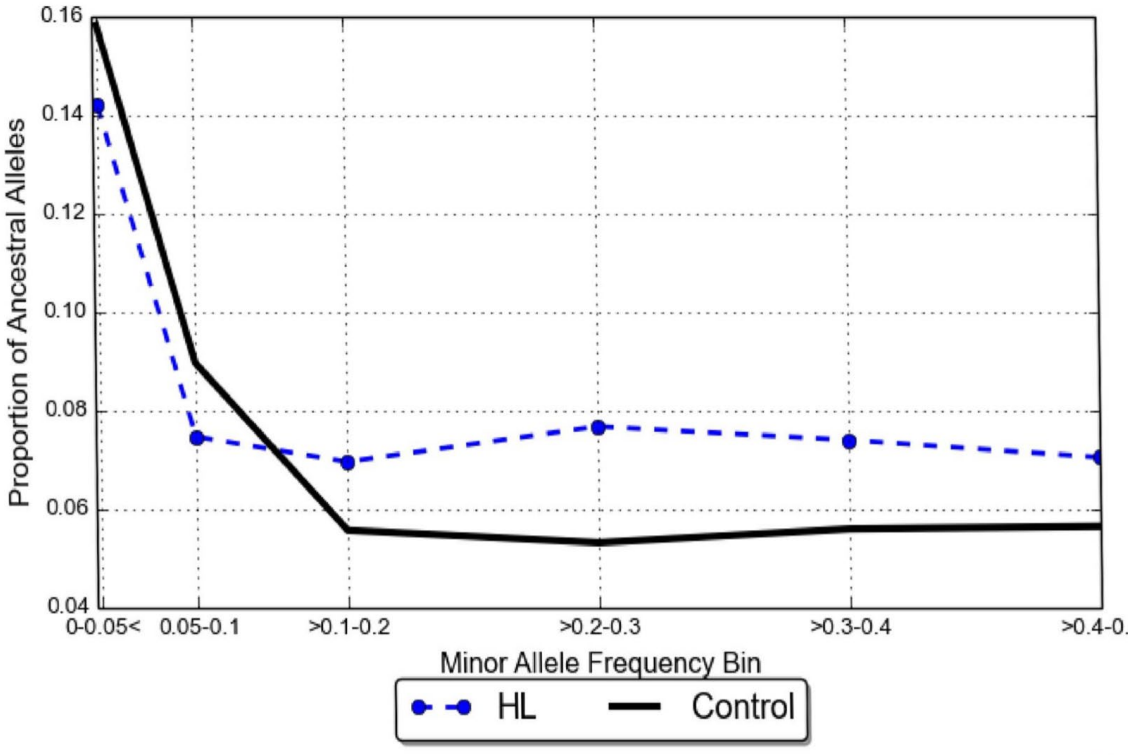


A)



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Human Molecular Genetics, 2020, Vol. 29, No. 23 3729–3743

doi: 10.1093/hmg/ddaa225
Advance Access Publication Date: 20 October 2020
General Article

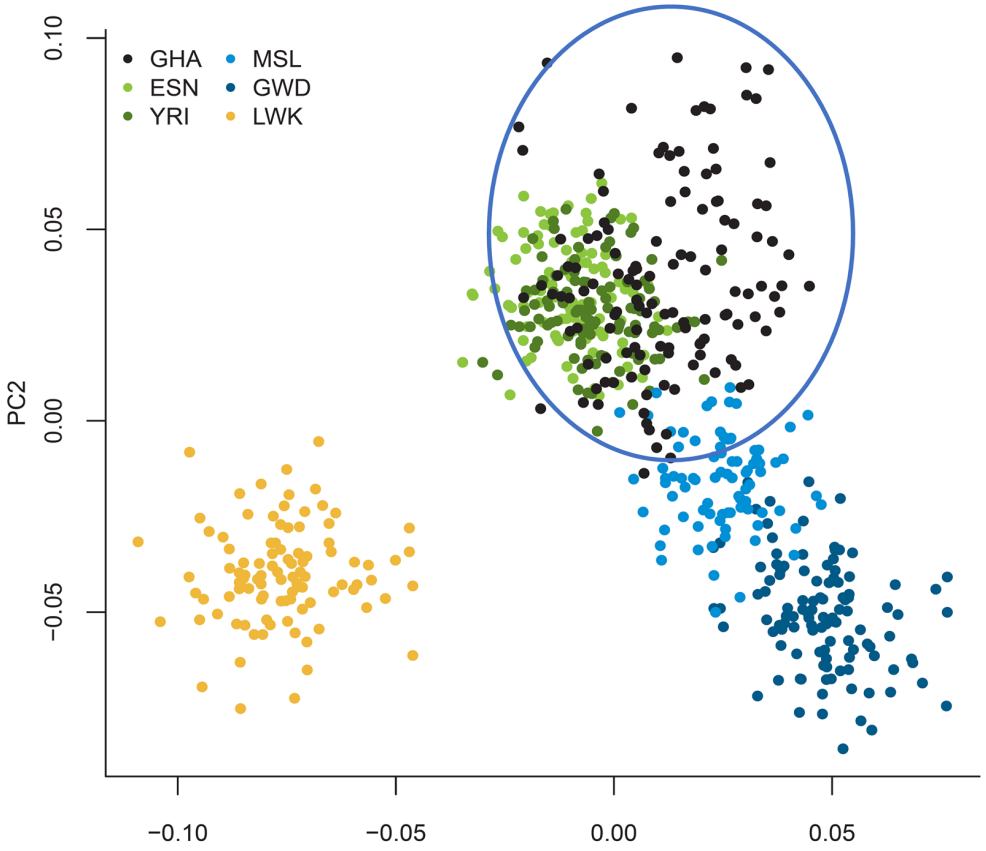
GENERAL ARTICLE

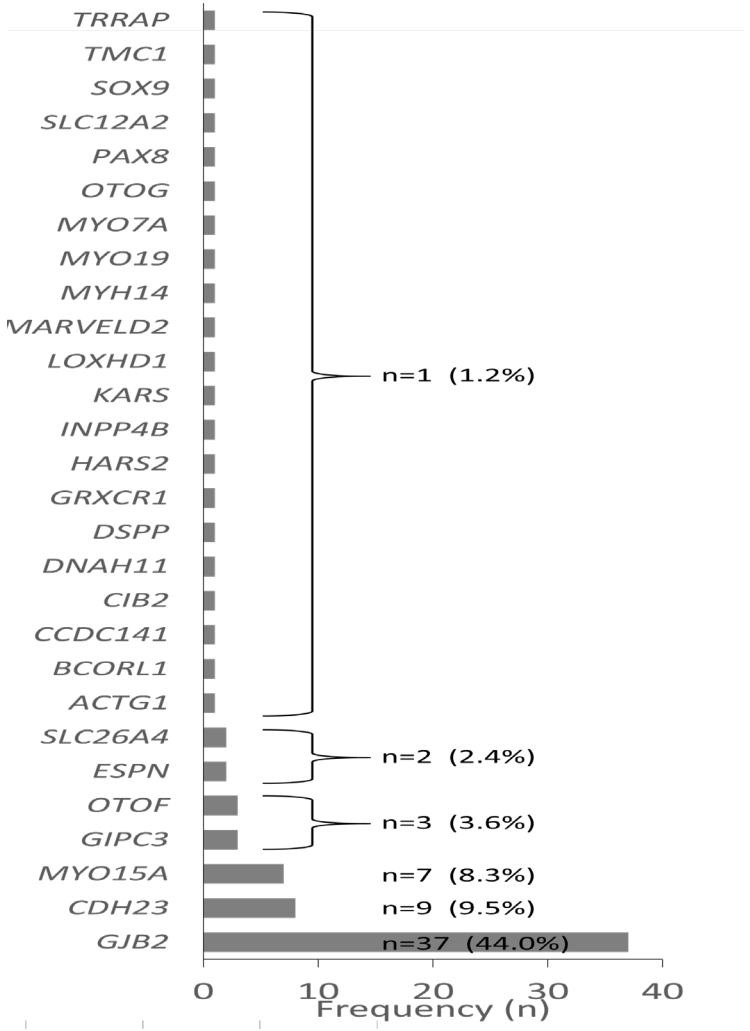
Whole exome sequencing reveals pathogenic variants in *MYO3A*, *MYO15A* and *COL9A3* and differential frequencies in ancestral alleles in hearing impairment genes among individuals from Cameroon

Ambroise Wonkam[1,2,*,†,‡], Noluthando Manyisa[1,‡], Christian D. Bope[3], Collet Dandara[1] and Emile R. Chimusa[1]

Genetics of Hearing Impairment in Ghana

B

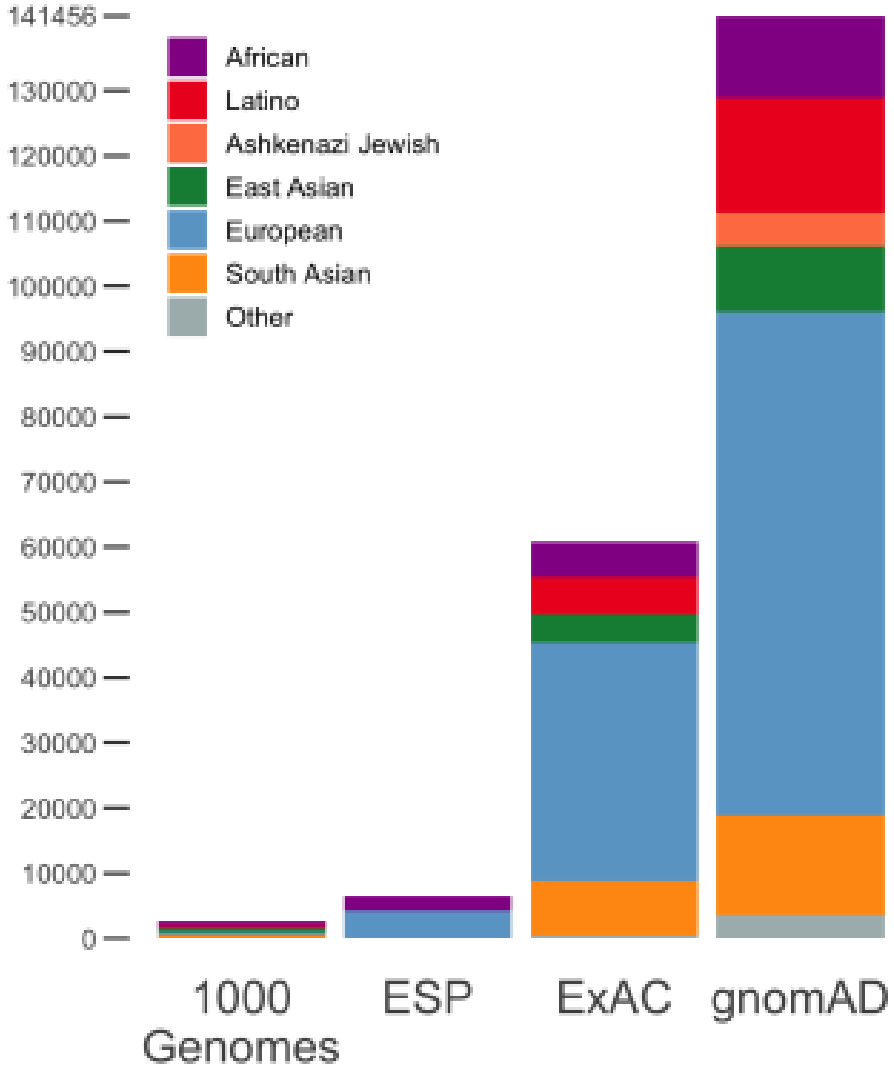




- High-resolution rate of 88.5% using WES
- *MYO15A* and *CDH23* the most common in *GJB2* negative families
- 62.3% of variants in known genes not previously associated with HI
- **Height novel candidate genes**

Waardenburg Syndrome: Novel *PAX*…Gene

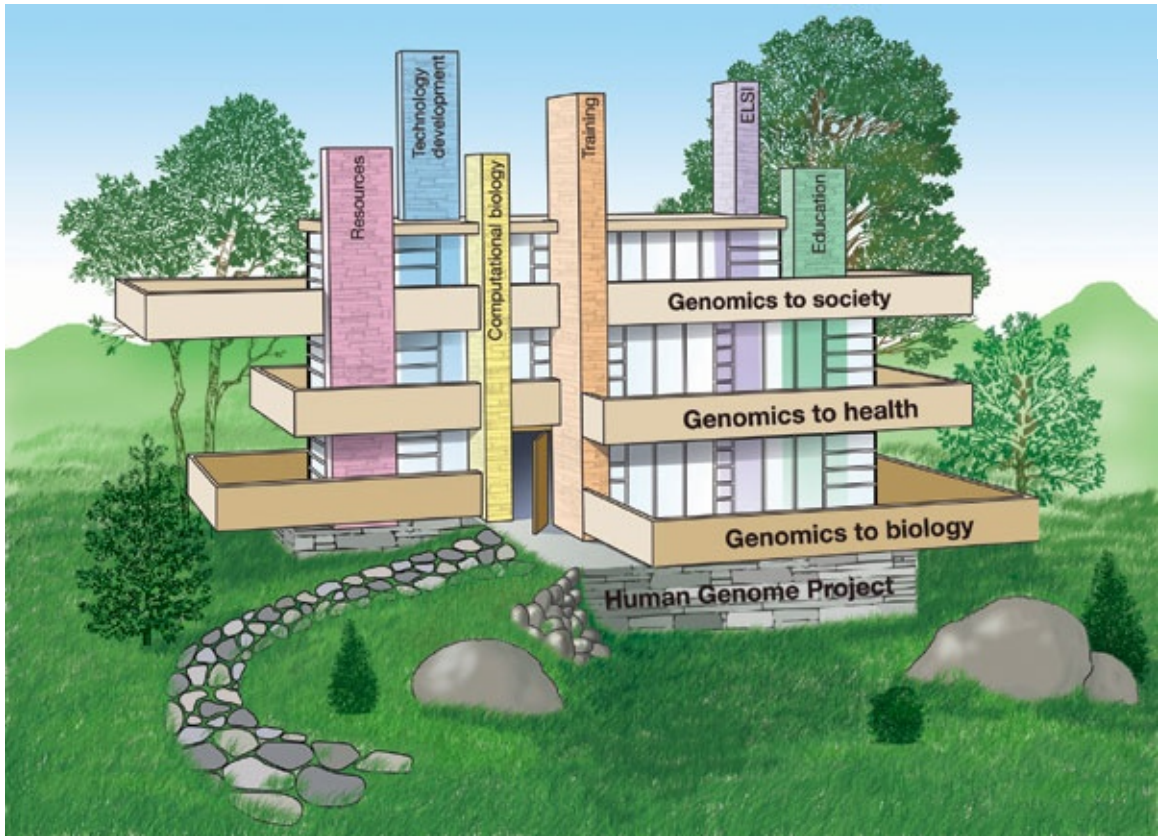
Addressing the Exome DB Diversity



Nature. 2016 August 18; 536(7616): 285–291.

The road ahead in genetics and genomics

Amy L. McGuire, Stacey Gabriel, Sarah A. Tishkoff, Ambroise Wonkam,



NATURE REVIEWS | GENETICS

African ancestry and ecosystems motivate investments in African genomic variations, as a scientific imperative,

with equitable access being a challenge to be addressed, to fully meet the potential of the next frontier of global genetic medicine.

Sequence three million genomes across Africa

Ambroise Wonkam

Capture the full scope of variation to improve health care, equity and medical research globally.

Two decades after the completion of the Human Genome Project (HGP), there is still much to do to ensure that genomics works for the global public good. The focus on populations from high-income countries has come at the cost of understanding health and disease that might benefit the world. Less than 2% of human genomes analysed so far have been those of African people[1], despite the fact that Africa, where humans originated, contains more genetic diversity than any other continent. Too little of the knowledge and applications from genomics have benefited the global south because of inequalities in health-care systems, a small local research workforce and lack of funding.

The African Society of Human Genetics (AfSHG), which I currently lead, was established in 2003 to help address disparities, improve education, enhance networking and build research capacity in Africa (www.afshg.org). Despite recent progress and investments, too much of the genomic research done in Africa has been driven by European and American investigators[2]. Why is this a problem? Their priorities could be detached from what people on the continent need and want. Testing new cover ethnolinguistic, regional and other groups. Therefore, we aim to start such a project, called the Three Million African Genomes (3MAG), which would build capacity on the continent — in genomics research and its applications, and governance. The findings would bring benefits worldwide, including some that are hard to anticipate. In a similar way, much knowledge put to use during the COVID-19 pandemic — from public communication to sharing biological samples and data — was hammered out in Ebola outbreaks during the past few years.

The development of 3MAG will probably take around a decade. We estimate core funding would need to be roughly $450 million per year (about $1,500 per participant). That would cover setting up and running biorepositories and developing data infrastructure and technology. We plan on sequencing and phenotyping about 300,000 African genomes in the first year.

Those who think this too daring are forgetting the ambition required to launch the HGP. That took more than 13 years, and infused genetic science across all areas of health care. Today, the cost of sequencing a genome is less than $1,000 — building the first draft reference genome cost around $300 million (see go.nature.com/3pfy2kh). Thirty years

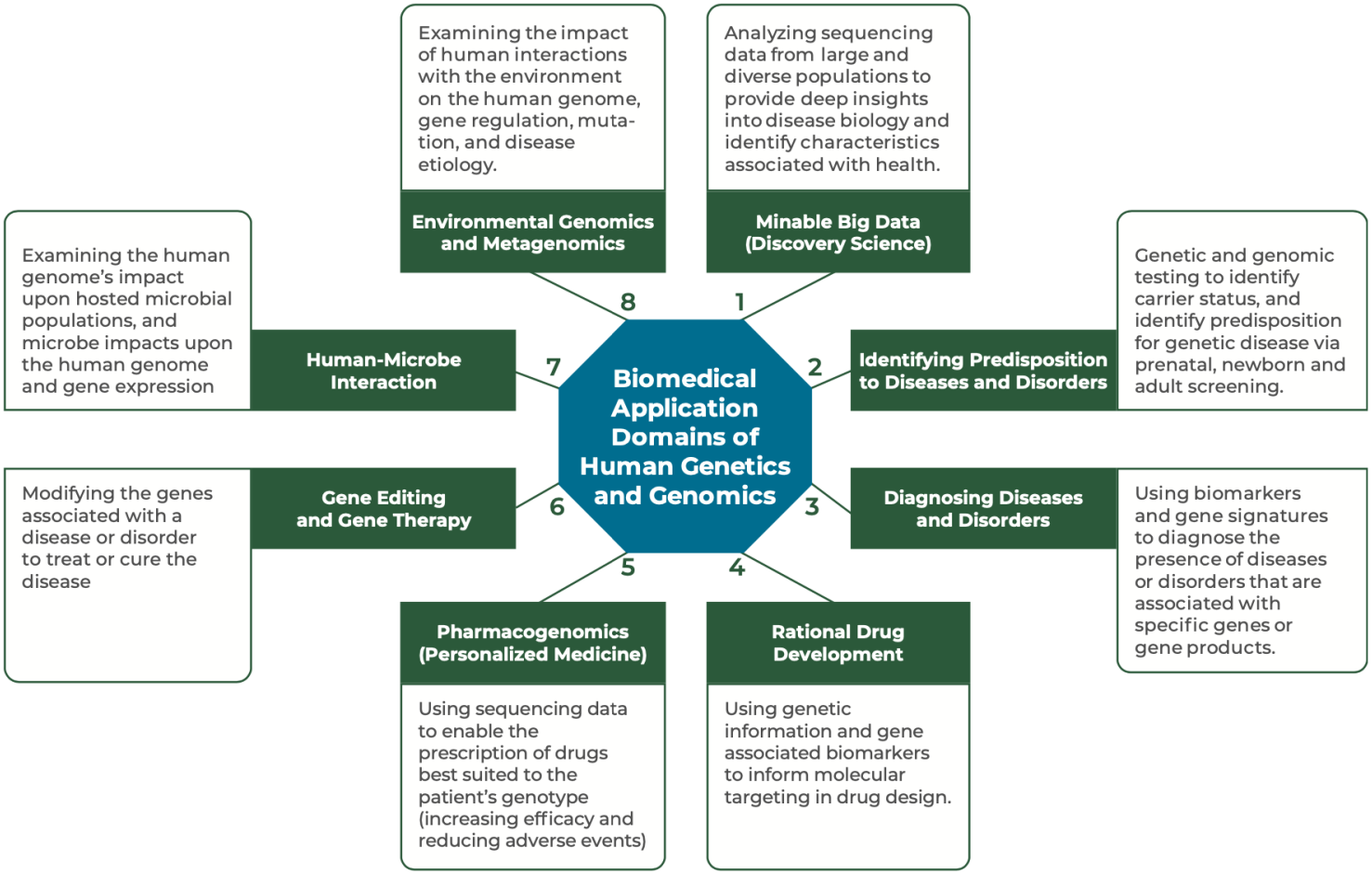
PAVING THE WAY: THREE MILLION AFRICAN GENOMES CAN DRAW FROM EXISTING PROJECTS

Programmes	Launch (duration)	Funding	Purpose	Products
Human Heredity and Health in Africa (H3Africa)	2011 (10 years)	US$180 million, US National Institutes of Health (NIH), Wellcome (partnership with the African Society of Human Genetics)	Builds collaborations and genetics research led by African scientists for Africans.	Genome-wide and sequencing data on 79,254 individuals across 30 African countries. Three Biorepositories (Nigeria, Uganda and South Africa).
Malaria Genomic Epidemiology Network (MalariaGEN)	2005 (ongoing)	Wellcome, UK Medical Research Council, Bill & Melinda Gates Foundation, NIH	Connects genomics researchers with clinicians in malaria-endemic countries.	Genome-wide data on 17,000 individuals from 39 countries (12 in Africa).
Harnessing Data Science for Health Discovery and Innovation in Africa (DS-I Africa)	2020 (5 years)	$58 million, NIH	Advances data science in Africa to benefit clinical care, public health and research.	Pending
Trans-Omics for Precision Medicine (TOPMed)	2014 (ongoing)	NIH	Integrates sequencing, molecular and clinical data to individualize treatments.	>90,000 whole genomes sequenced and genome-wide data for 155,000 individuals from >80 different studies; 47,020 participants of African ancestry.
Genome Aggregation Database (gnomAD)	2017 (ongoing)	Broad Institute	Aggregates and harmonizes data from large sequencing projects in a public portal	>140,000 exomes (protein-encoding regions) and genomes from a variety of sequencing projects; 20,744 African/ African American participants.
UK Biobank	2006 (ongoing)	$332.3 million (multiple UK agencies)	Provides biomedical and genetic data from many individuals for medical research.	Clinical and genome-wide data from 500,000 participants, 8,066 Black African; 200,000 participant exomes.

The Economic Impact and Functional Applications of Human Genetics and Genomics

Commissioned by the American Society of Human Genetics
Produced by TEConomy Partners, LLC.
Report Authors: Simon Tripp and Martin Grueber

May 2021



$3.3B
FEDERAL RESEARCH

152,000
INDUSTRY JOBS

850,000
TOTAL SUPPORTED JOBS

$265B
TOTAL ECONOMIC IMPACT

$5.2B
DIRECT FEDERAL TAX REVENUES

4.75:1.00
FEDERAL RETURN ON INVESTMENT

ASANTE SANA/ENKOSI/THANKS!

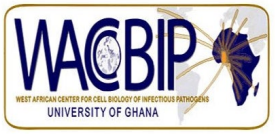
HIGeneSAfrica
Hearing Impairment Genetics Studies in Africa

NIH: 1.25 million USD (PD/PI)
AESA/Wellcome trust: 2.07million USD
1 U01 HG009716-01
Ref: H3A/18/001

IFGeneRA
Individual Findings in Genomics Research in Africa

NIH: 2.6 million USD (PD/PI)
1U54HG009790-01

GeneMAP
Genetic Medicine of African Populations



Wellcome Trust- DELTAS (Co-I)
1/5 million USD (Parent grant: 7.2 million USD)
Ref: 107755Z/15/Z

NIH 4.3 million USD (PD/PI)
1 U24 HL135600-01
1 U01 HG007459-01